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ABOUT COVER

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AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc*.

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EDITORIAL

New Year's greeting and overview of *World Journal of Critical Care Medicine* in 2021

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Abstract

As editors of *World Journal of Critical Care Medicine* (*WJCCM*), it is our great pleasure to take this opportunity to wish all our authors, subscribers, readers, Editorial Board members, independent expert referees, and staff of the Editorial Office a Very Happy New Year. On behalf of the Editorial Team, we would like to express our gratitude to all authors who have contributed their valuable manuscripts and to the independent referees and our subscribers and readers for their continuous support, dedication, and encouragement. The excellent team effort by our editorial board members and staff of the Editorial Office allowed *WJCCM* to advance remarkably in 2020. In the future, the Baishideng Publishing Group and *WJCCM*'s editorial board will continue to increase their communication and collaboration, both internally and involving our external contributors, in order to promote our collective impact on the field of Critical Care Medicine even further.

Key Words: Acknowledgments; Editorial members; *World Journal of Critical Care Medicine*; Baishideng Publishing Group; Journal development

Core Tip: As editors of the *World Journal of Critical Care Medicine* (*WJCCM*) and in view of the achievements of this journal in 2020, we take this opportunity to wish all our authors, subscribers, readers, Editorial Board members, independent expert referees, and staff of the Editorial Office a Very Happy New Year and express our gratitude to your collective and individual contributions and support. In the future, the Baishideng Publishing Group and the *WJCCM*'s editorial board will continue to work to strengthen further communication and cooperation within the field of critical care medicine and emergency medicine, while simultaneously promoting the development

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INTRODUCTION

First of all, we, on behalf of all editors of the Baishideng Publishing Group (BPG), extend our sincere gratitude to you for your contributions to the *World Journal of Critical Care Medicine* (*WJCCM*) in 2020. We wish you a Happy New Year!

In 2020, BPG routinely published 47 open-access journals, including 46 English-language journals and 1 Chinese-language journal. Our successes were accomplished through the collective dedicated efforts of BPG staff and Editorial Board Members, such as yourself. BPG's Editorial Board Members number 3136, and Peer Reviewers number 29039.

ACADEMIC INFLUENCE OF *WJCCM*

As one of the key developing journals of BPG, *WJCCM* was founded in 2012 as a high-quality, online, open-access, single-blind, peer-reviewed journal published by the Baishideng Publishing Group[1]. The journal has a total of 31 official editorial board members[2], and their country distribution is shown in Figure 1. *WJCCM* mainly publishes articles reporting research results obtained in the field of critical care medicine and covering a wide range of topics, including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, intensive care unit management and treatment control, infection and anti-infection treatment, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, severe infection, and shock and multiple organ dysfunction syndrome. While we are celebrating *WJCCM*'s 9-year anniversary, we are very proud to share with you that since its launch, *WJCCM* has published 155 articles (Figure 2). Among these, the total cites is 1738, and the average cites per article is 11.21 (Figure 3). The current number of total visits to the *WJCCM* homepage is about 370000, of which 20.6% of those visits have been from the United States, 17.7% from Bosnia and Herzegovina, and 9.6% from China. The specific traffic data and download statistics are shown in Figure 4A and B. The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure, China Science and Technology Journal, and Superstar Journals databases[2]. BPG will be submitting an application to Clarivate Analytics in 2022, with anticipation of it being abstracted and indexed in the Science Citation Index Expanded.

In 2020, *WJCCM* received a total of 23 manuscripts from authors around the world for consideration of publication and published nine articles[3]. The distribution of published manuscripts by type is shown in Figure 5. The distribution of authors of published articles by country/territory is shown in Figure 6.

In the last month of 2020, we received 68 manuscripts for consideration for publication in 2021 following successful completion of peer-review. The specific types and number of manuscripts received are shown in Figure 7A and B. As a global academic journal in critical care medicine, our authors hail from various countries and regions, reflecting a diversified contribution to the field that is embodied within an optimized platform to promote worldwide medical research sharing and exchange.

All the good achievements that were made in the past year are inseparable from the dedication of our authors, subscribers, readers, Editorial Board members, independent expert referees, and staff of the *WJCCM*'s Editorial Office. To date, *WJCCM* has 31 official editorial board members. We hope that each *WJCCM* Editorial Board Member will continue to conduct high-quality peer reviews for *WJCCM* in 2021 and support

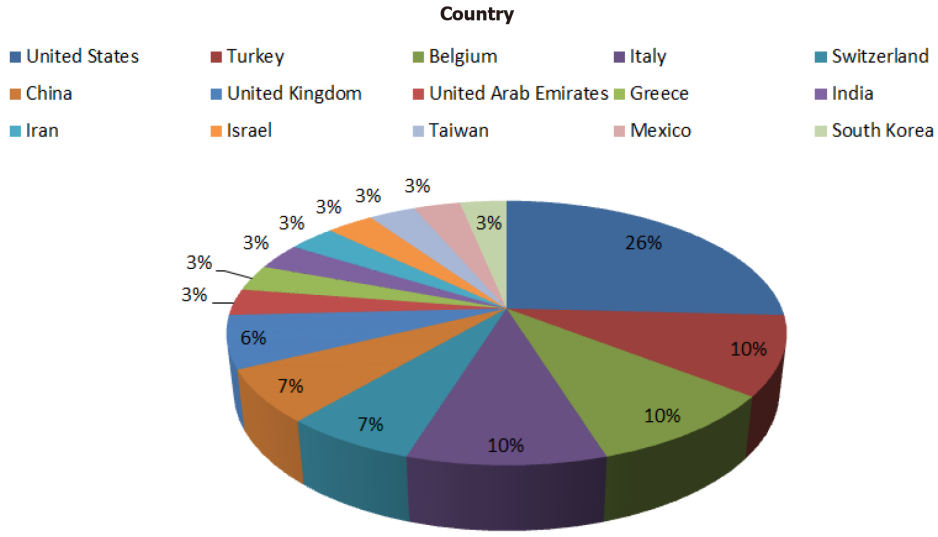

Figure 1 Distribution of Editorial Board members' countries for *World Journal of Critical Care Medicine*.

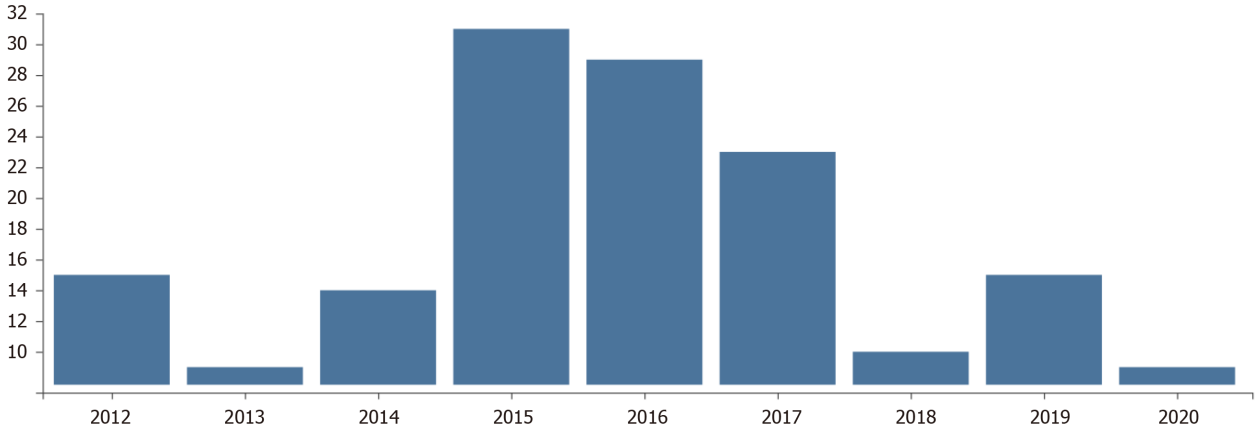

Figure 2 Analysis of the number of articles published since 2012.

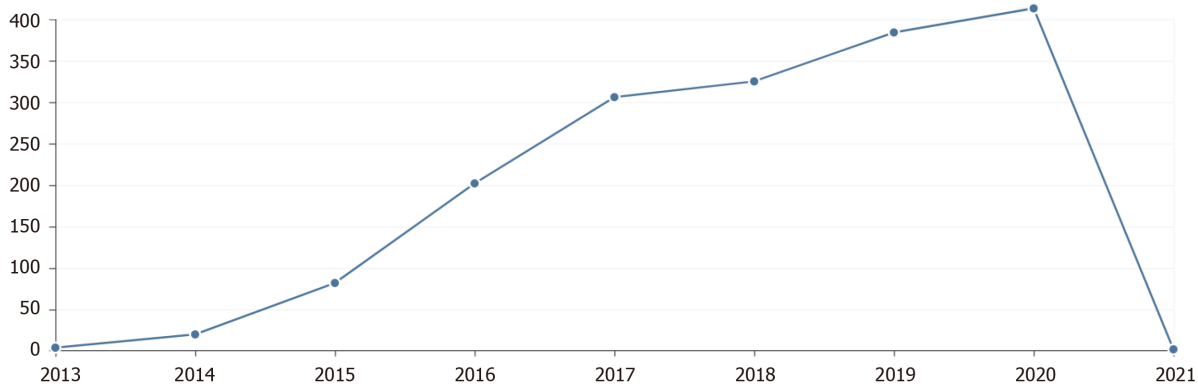

Figure 3 According to the year of publication, the citation frequency of the article.

WJCCM's mission of publishing high-quality articles that will make substantive contributions to the development of basic medical and clinical research. Meanwhile, we hope that every expert in the field of critical care medicine will contribute more articles to support our efforts towards that end. We look forward to more outstanding experts and scholars actively applying to become members of our editorial department. As always, all peer review experts are urged to review each manuscript in a timely

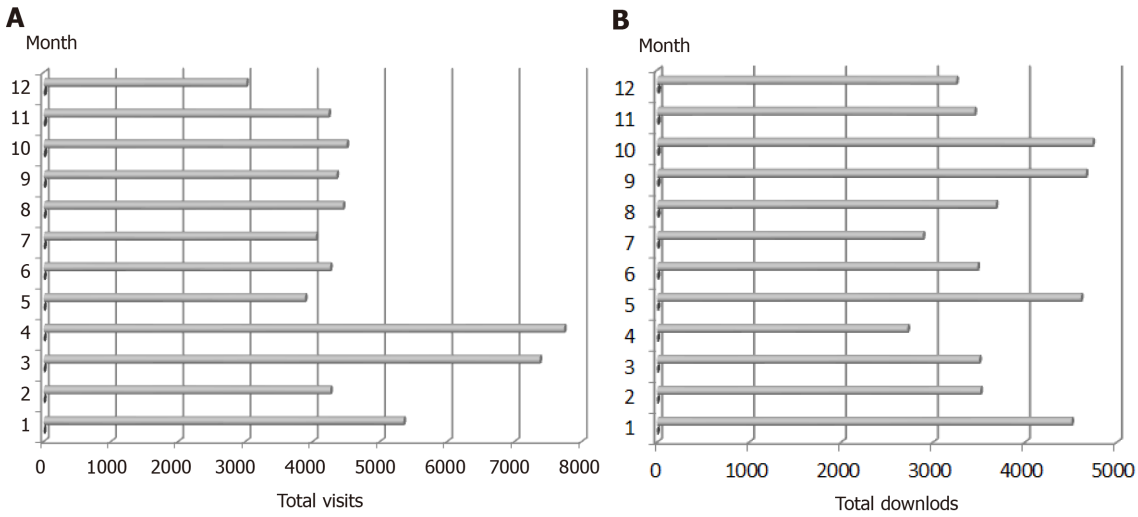

Figure 4 Number of total visits to the *World Journal of Critical Care Medicine* homepage and number of total downloads to the *World Journal of Critical Care Medicine* articles in 2020. A: Total visits; B: Total downloads.

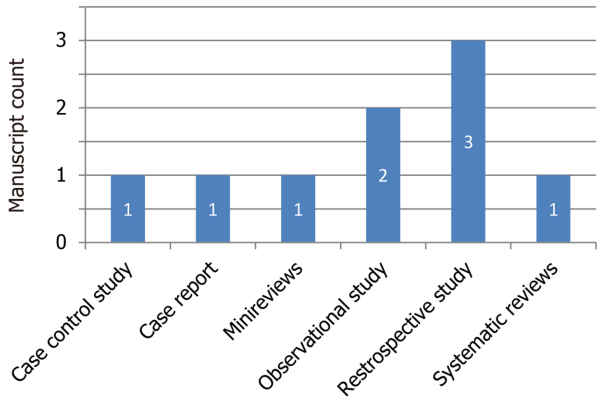

Figure 5 Column type distribution of manuscripts published in *World Journal of Critical Care Medicine* in 2020.

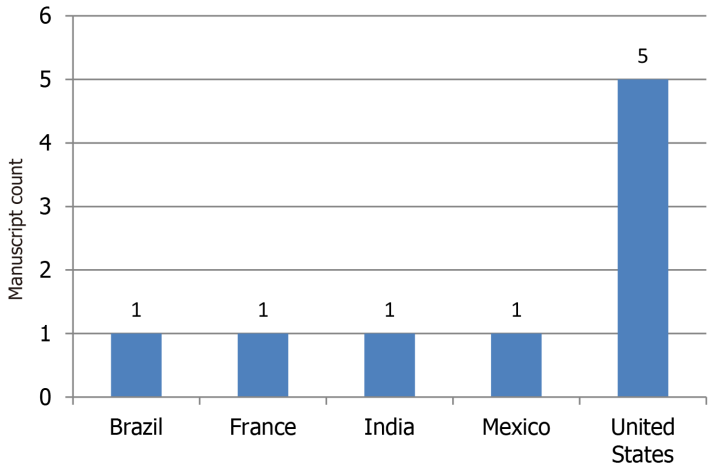

Figure 6 Distribution of authors' countries for the manuscripts published in *World Journal of Critical Care Medicine* in 2020.

manner.

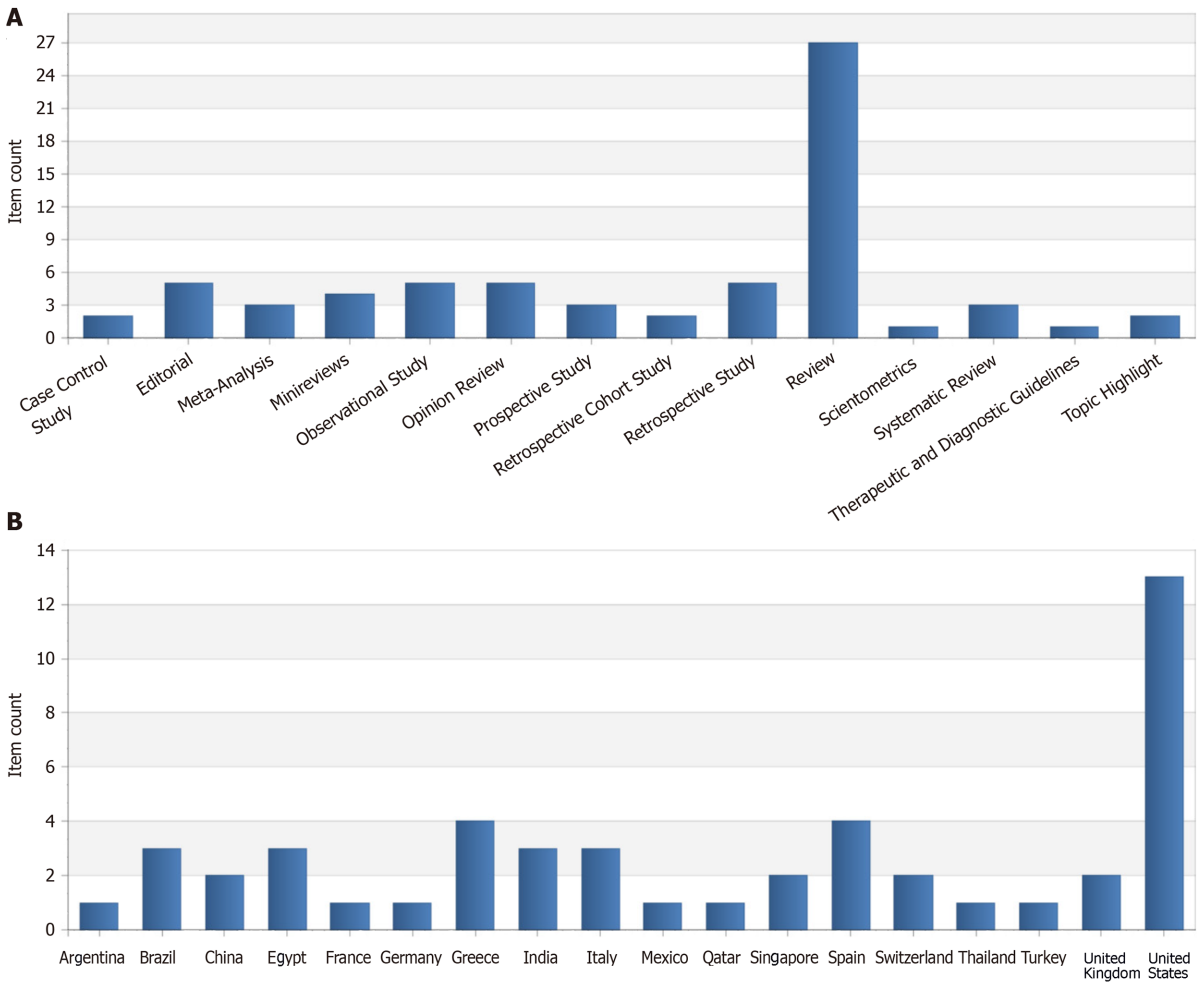

Figure 7 Bibliographic data for articles received by the *World Journal of Orthopedics* in the last month of 2020. A: Article types; B: Authors' countries.

CONCLUSION

It is with your great support that we expect to be more productive and to be able to raise the academic rank of *WJCCM* even higher in order to achieve these goals, we appreciate the continuous support and submissions from authors and the dedicated efforts and expertise by our invited reviewers, many of who also serve on our editorial board. The Editors-in-Chief will continue to strive to work with the journal's Editorial Office staff to make the manuscript submission process as simple as possible and to ensure efficient communication with the authors, providing professional support and answering their questions. Ultimately, we will remain open to any suggestions that could improve *WJCCM*'s operation and publication. Please feel free to contact us (editorialoffice@wjgnet.com) if any question on your personal submission arises or you have any suggestions.

Once again, on behalf of *WJCCM*, we wish you and your families the best for the New Year.

REFERENCES

1 **Baishideng Publishing Group**. The home page of *World Journal of Critical Care Medicine*. Available from: https://www.wjgnet.com/2220-3141/index.htm
2 **Baishideng Publishing Group**. Editorial Board Members. Available from: https://www.wjgnet.com/2220-3141/editorialboard.htm
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REVIEW

Sepsis: Evidence-based pathogenesis and treatment

Jay Pravda

ORCID number: Jay Pravda 0000-0001-5737-5506.

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Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Jay Pravda, Inflammatory Disease Research Centre, Therashock LLC, Palm Beach Gardens, FL 33410, United States

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Abstract

Sepsis can develop during the body's response to a critical illness leading to multiple organ failure, irreversible shock, and death. Sepsis has been vexing health care providers for centuries due to its insidious onset, generalized metabolic dysfunction, and lack of specific therapy. A common factor underlying sepsis is the characteristic hypermetabolic response as the body ramps up every physiological system in its fight against the underlying critical illness. A hypermetabolic response requires supraphysiological amounts of energy, which is mostly supplied *via* oxidative phosphorylation generated ATP. A by-product of oxidative phosphorylation is hydrogen peroxide (H_2O_2), a toxic, membrane-permeable oxidizing agent that is produced in far greater amounts during a hypermetabolic state. Continued production of mitochondrial H_2O_2 can overwhelm cellular reductive (antioxidant) capacity leading to a build-up within cells and eventual diffusion into the bloodstream. H_2O_2 is a metabolic poison that can inhibit enzyme systems leading to organ failure, microangiopathic dysfunction, and irreversible septic shock. The toxic effects of H_2O_2 mirror the clinical and laboratory abnormalities observed in sepsis, and toxic levels of blood H_2O_2 have been reported in patients with septic shock. This review provides evidence to support a causal role for H_2O_2 in the pathogenesis of sepsis, and an evidence-based therapeutic intervention to reduce H_2O_2 levels in the body and restore redox homeostasis, which is necessary for normal organ function and vascular responsiveness.

Key Words: Sepsis; Septic shock; Redox homeostasis; Thiosulfate; Hydrogen peroxide

Core Tip: Sepsis mortality remains unacceptably high because there is no specific treatment to prevent or reverse the multiple organ failure and refractory hypotension that develops in this condition. An evidence-based analysis suggests that impaired

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systemic redox homeostasis caused by the toxic accumulation of hydrogen peroxide has a causal role in the pathogenesis of this often fatal illness. The data imply that restoration of redox homeostasis by therapeutic reduction of hydrogen peroxide will significantly reduce the morbidity and mortality associated with sepsis. A therapeutic intervention to reduce systemic levels of hydrogen peroxide is presented.

Citation: Pravda J. Sepsis: Evidence-based pathogenesis and treatment. *World J Crit Care Med* 2021; 10(4): 66-80
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INTRODUCTION

Medicine has made fantastic strides over the past century. Our intricate knowledge of disease has been spearheaded by amazing advances in laboratory techniques that allow us to identify and instigate changes at the molecular level. This has led to an explosion of data accompanied by a detailed insight into pathological processes that perpetuate disease states leading to the identification of potential therapeutic targets, which can be exploited for new and more effective therapeutic interventions. However, while laboratory research is an extremely useful tool to obtain a pathophysiological snapshot of disease it cannot, on its own, identify the pathogenesis, and for some diseases, a creative theoretical approach is the only way to get "upstream" where novel insights may shed light on difficult clinical problems.

A prime example is sepsis, a systemic process with a high fatality rate that ultimately leads to microangiopathic dysfunction, refractory hypotension, multiple organ failure, and death. Worldwide, someone dies of sepsis every 3 s with 20% of global deaths being sepsis-related for a total of 11 million deaths annually and growing. Sepsis is thought to be a hyper-immune response to infection[1]. But in over 40% of sepsis cases there is no identifiable infectious agent, and culture positivity is not independently associated with mortality in sepsis[2-6]. These observations suggest that infection can be sufficient but is not absolutely necessary for sepsis to develop. It also suggests an endogenous process that is common to both infectious and non-infectious conditions (*i.e.*, multiple body trauma, pancreatitis, post-surgery, *etc.*), which is set in motion, ultimately leading to sepsis. Finally, the profound immunosuppression occurring during sepsis[7] suggests a non-immune contemporaneous process as the proximate causal factor in the development of the sepsis syndrome. This raises the consideration that the immune system is failing for the same reason other organs fail.

From a metabolic perspective, there is evidence of impaired mitochondrial oxygen utilization in sepsis despite normal oxygen tension[4,8-10]. This suggests a mitochondrial-derived agent capable of interfering with oxygen utilization by inhibiting substrate oxidation during the tricarboxylic acid (Krebs) cycle or oxidative phosphorylation. The close association of hyperlactatemia with adverse sepsis outcomes despite the absence of tissue hypoxia or impaired tissue oxygenation provides further evidence that implicates impairment of mitochondrial oxidative metabolism as discussed in more detail below[11,12].

The identification of mitochondrial abnormalities in sepsis focuses attention on bioenergetics and suggests that the common link between infectious and non-infectious origins of sepsis is not an immune response but a hypermetabolic state that sends mitochondrial metabolism into “overdrive” causing dysfunction of vital intramitochondrial bioenergetic processes. This reduces the problem of sepsis to the identification of a mitochondrial-generated molecule whose production is scaled up during hypermetabolism and is capable of inhibiting enzymes in the Krebs cycle and/or the electron transport chain (ETC). This is likely to be a small molecule that is normally eliminated within mitochondria since most people do not develop sepsis during a clinical hypermetabolic response.

A prime element that fulfills these theoretical requirements is hydrogen peroxide (H_2O_2), a small, cell-membrane permeable highly toxic oxidizing agent that is produced within mitochondria as a result of electron transport chain auto-oxidation [13]. H_2O_2 must be immediately eliminated to prevent cell damage and is removed by

the following series of reactions (Figure 1)[14-16].

Studies have shown that blood H_2O_2 is significantly elevated in human sepsis and septic shock with values reported up to 558 μmol/L, which is over 100 times the normal upper limit of 5 μmol/L and over ten times 50 μmol/L upper limit at which H_2O_2 becomes cytotoxic[17-19]. Certain cell populations, such as lymphocytes, undergo apoptosis at H_2O_2 exposure of less than 1 μmol/L, which can lead to significant lymphopenia and immunosuppression[19,20]. Normal intracellular H_2O_2 levels are in the picomolar range[19,21]. Thus, septic blood has over a million times greater H_2O_2 concentration than normal cells resulting in the potential for significant systemic cellular cytotoxicity which can disrupt metabolic pathways and organ function.

Other clinical abnormalities observed in sepsis such as hypotension, coagulopathy, encephalopathy, microangiopathic and cardiac dysfunction, erythrocyte rigidity, methemoglobinemia, glutathione depletion, mitochondrial damage, and lymphocyte apoptosis are also documented adverse effects of H_2O_2, all of which contribute to multiple organ failure and lymphocytopenia observed in sepsis[22-25].

But where does all this H_2O_2 come from? Although leukocytes such as neutrophils can produce large amounts of H_2O_2 during the respiratory burst[26], the profound immunosuppression[7,27-30] during advanced stages of sepsis suggests a significant non-immune contribution to the persistently elevated blood H_2O_2 levels observed in advanced sepsis and septic shock. Significant depletion of tissue glutathione in muscle, lung, and erythrocytes in addition to plasma thiol depletion (albumin cys34) suggests these tissues have become H_2O_2 generators contributing to elevated blood H_2O_2 in sepsis patients[22,31,32].

The production of mitochondrial H_2O_2 depends upon the rate of electron transfer through the ETC. The higher the electron transfer rate the greater the production of H_2O_2. Studies in isolated mitochondria have shown an exponential increase in reactive oxygen species (*i.e.*, H_2O_2) at strongly polarized levels of mitochondrial membrane potential[33], which can occur in hypermetabolic critically ill patients. Other studies in mice have shown that mitochondrial H_2O_2 will increase up to 15x the normal rate during state-3 (maximal) respiration[34]. The clinical correlate of state-3 respiration is a hypermetabolic state, which is characterized by tachycardia, tachypnea, leukocytosis, high fever, and significantly enhanced protein biosynthesis. These are the cardinal elements that define the systemic inflammatory response syndrome (SIRS), which accompanies sepsis. This implies that a clinical hypermetabolic response is accompanied by supraphysiological increases in ETC-generated H_2O_2 and is the common factor linking infectious and non-infectious sepsis.

Due to the limited amount of mitochondrial glutathione available for H_2O_2 neutralization in addition to high basal levels of mitochondrial H_2O_2, a sustained hypermetabolic response can overwhelm cellular reductive (antioxidant) capacity resulting in un-neutralized H_2O_2 leaking out of cells and into the bloodstream with a subsequent rise in blood H_2O_2 reaching toxic levels[35-40].

H_2O_2 is a metabolic poison and the data suggest that sepsis is due to an endogenous H_2O_2 poisoning secondary to the oxidative damage inflicted by this highly toxic oxidizing agent. Since H_2O_2 is permeable through cell membranes, elevated blood H_2O_2 indicates systemic reductive depletion, which perpetuates the production of H_2O_2 [41]. Toxic levels of H_2O_2 will disrupt cellular function in all body organs, which can lead to multiple organ failure and microvascular dysfunction. Any cell undergoing a hypermetabolic response can deplete its reductive capacity and contribute to total body H_2O_2 load.

A potential cause and effect relationship between H_2O_2 and sepsis has likely remained obscure because a hypermetabolic state, which generates H_2O_2, is a confounding factor in the relationship between infection and sepsis (Figure 2)[42-51].

Based on the data, H_2O_2 is also an intervening variable in the setting of critical illness-associated sepsis (Figure 3)[52-55]. Intervening variables have an important role in therapy as they are mechanistically "closer" to the final effect and can serve as a therapeutic target. The observation that culture-positive sepsis patients on appropriate antibiotics still die suggests an additional factor independent of infection that exerts a significant influence on the clinical outcome of sepsis[5]. In this scenario, the H_2O_2 induced tissue damage and metabolic dysfunction (the effect) is too severe and can no longer be reversed by treating the infection (the exposure) with antibiotics. As an intervening variable with a postulated causal role in sepsis, H_2O_2 explains why culture positivity is not independently associated with mortality in sepsis[5] since the data supports H_2O_2 (and not infection per se) as the proximal causal agent in sepsis.

Figure 1 Krebs cycle derived reducing equivalents (NADH, FADH2) donate electrons that are processed by the electron transport chain during oxidative phosphorylation. Up to 5% of electrons (e^-) will normally escape the electron transport chain (ETC) into the mitochondrial matrix (electron leakage)[14-16]. These electrons combine with molecular oxygen (O_2) to form superoxide anion radical (O_2^-), which is metabolized by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2) that in turn is converted to glutathione disulfide (GS-SG) and water *via* glutathione peroxidase (GPX) and its reducing co-factor glutathione (GSH). Critical illness hypermetabolic states increase ETC activity leading to enhanced electron leakage and far greater H_2O_2 formation, which can deplete cellular GSH resulting in a build-up of H_2O_2 in cells and blood causing bioenergetic dysfunction and organ failure.

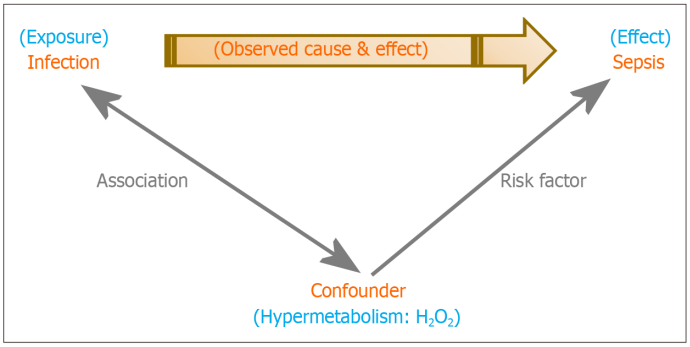

Figure 2 Confounding in Sepsis: The hypermetabolic state that accompanies a critical illness is a con-founding factor in the relationship between systemic infection (exposure) and sepsis (effect). Hypermetabolism generates large amounts of hydrogen peroxide (H_2O_2), which is both a risk factor for the development of sepsis and is bilaterally associated (double arrow) with infection. Systemic infection triggers a hypermetabolic state accompanied by greatly amplified generation of H_2O_2, but non-infectious critical illness can also generate large amounts of H_2O_2 due to the accompanying hypermetabolic state. High levels of blood H_2O_2 can cause systemic lymphocyte apoptosis leading to significant lymphocytopenia, which predisposes to infection. Thus, systemic build-up of H_2O_2 can lead to sepsis. This can occur after an infectious or non-infectious insult. In the latter instance, infection may develop as a result of H_2O_2 induced systemic lymphocyte apoptosis and subsequent lymphocytopenia.

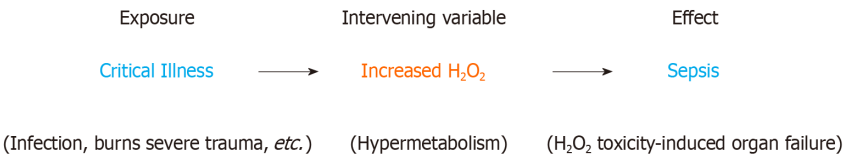

Figure 3 Sepsis and intervening variables: Hydrogen peroxide is an intervening variable between a critical illness (exposure), which triggers a systemic hypermetabolic response, and sepsis (effect). Hypermetabolism, characterized by the systemic inflammatory response syndrome, is the clinical manifestation of supraphysiological cellular H_2O_2 production. This will eventually lead to reductive depletion and sepsis (H_2O_2 toxicity, bioenergetic organ failure) if allowed to persist. Prolonged critical illness (hypermetabolism) and dietary restriction severely limit the body's ability to re-establish and maintain redox homeostasis. Under these circumstances, direct acting reducing equivalents must be supplied to the patient to aid in neutralizing excess H_2O_2. A hypermetabolic response to critical illness or injury may continue for years after hospital discharge and contribute to increased inpatient and post-discharge morbidity and mortality (chronic critical illness and post sepsis syndrome respectively)[52-55].

All hypermetabolic states (infectious and non-infectious), have the potential of generating excess H_2O_2, which can accumulate to toxic levels leading to bioenergetic organ failure and sepsis. The relationship between exposure (infection) and con-founder (H_2O_2) is bilateral because systemic infections cause a hypermetabolic state that can elevate blood H_2O_2 but non-infectious hypermetabolic states (*i.e.*, burns, multiple body trauma) can generate sufficient H_2O_2 leading to generalized lymphocyte apoptosis and profound lymphocytopenia, which can lead to infection. Serial negative blood cultures can eventually turn positive because of this phenomenon. In other words, infections can increase blood H_2O_2 but a primary non-infectious increase in blood H_2O_2 can eventually lead to infection, reinforcing the widely held view that sepsis is always due to infection. In the latter case, infection is the result of H_2O_2 induced lymphocytopenia (Figure 4).

Studies have shown that certain antibiotics can cause mitochondrial dysfunction accompanied by a significant production of H_2O_2[46]. This implies that patients must have sufficient residual reductive capacity to deal with the oxidative stress imposed by antibiotic treatment, underscoring the critical need to begin antibiotics along with

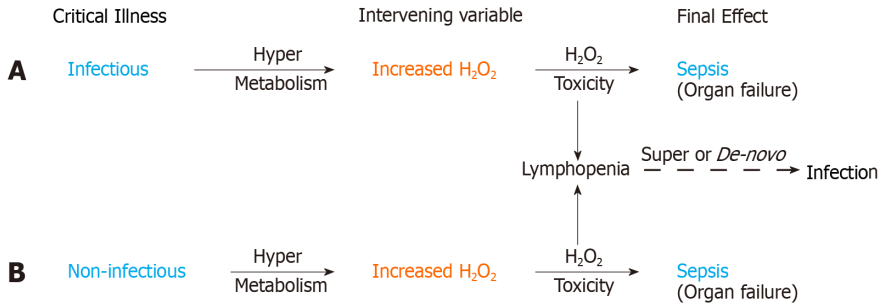

Figure 4 H_2O_2 induced immune system failure. Sequences 4A and 4B illustrate the common hypermetabolic response in infectious and non-infectious critical illness leading to H_2O_2 toxicity induced organ failure and sepsis. Lymphocytes are highly sensitive to H_2O_2 induced apoptosis. Lymphopenia is thus a manifestation of H_2O_2 induced immune system failure secondary to a hypermetabolic response in both infectious and non-infectious critical illness. H_2O_2 induced lymphopenia will predispose to de-novo infection in otherwise sterile critical illness and may cause a super-infection in patients on appropriate antibiotics. H_2O_2 toxicity and/or super-infection may contribute to sepsis mortality despite appropriate antibiotics.

reductive therapy as early as possible during the course of infection-associated sepsis. Reductive therapy encompasses any treatment that increases reductive (antioxidant) capacity, *i.e.*, glutathione, protein thiols, *etc.* The purpose of which (in sepsis) is to augment the patient's reductive (antioxidant) capacity to neutralize H_2O_2.

For the patient, the clinical benefits of limiting exposure to H_2O_2 go beyond discharge from the hospital because H_2O_2 can damage mitochondrial DNA. Mitochondrial DNA (mtDNA) is highly vulnerable to H_2O_2 induced oxidative damage due to the proximity of mtDNA to the electron transport chain, both of which reside on the matrix side of the inner mitochondrial membrane. Exposure of mtDNA to H_2O_2 will inflict base mutations and nucleotide mispairing that upon transcription result in the incorporation of mutated protein subunits into the electron transport chain (ETC). Mutated ETC components interfere with electron transport resulting in augmented electron leakage with increased H^2O^2 generation[47-52]. This establishes a self-amplifying vicious cycle with ever greater production of H_2O_2 and mtDNA damage, which can lead to prolonged metabolic and bioenergetic dysfunction in sepsis survivors and contribute to the post-sepsis syndrome.

H_2O_2 induced impaired redox homeostasis as a primary mechanism of disease is a novel pathogenesis that is supported by experimental evidence and is grounded in fundamental concepts of redox biology, redox biochemistry, and bioenergetics. Similar to electrolyte balance and acid/base buffering systems, redox homeostasis is a vital homeostatic mechanism required for normal cellular function and should be assessed in all critically ill patients.

CLINICAL MANIFESTATIONS OF H2O2 INDUCED OXIDATIVE STRESS

Since most H_2O_2 is a product of mitochondrial electron transport chain activity, clinical manifestations of H_2O_2 begin with its effects on cellular metabolism. Indeed, with almost 40% of all cellular reactions being redox reactions[53], the potential for H_2O_2 induced oxidative impairment of cellular metabolism and bioenergetics cannot be overstated, especially since blood H_2O_2 levels reported in sepsis exceed cellular cytotoxic tolerances by several-fold[17]. The mechanisms of H_2O_2 toxicity mirror the clinical manifestations of sepsis and include:

Hyperlactatemia

Elevated blood lactate is common among patients with sepsis and is associated with significantly greater mortality[12]. Toxic levels of H_2O_2 can inhibit enzymes in the Krebs cycle and electron transport chain leading to hyperlactatemia and bioenergetic failure characteristic of advanced sepsis[54-59]. H_2O_2 increases cellular lactate by interrupting mitochondrial oxidative energy flux (directional oxidation), which is needed to maintain the proton motive force (electrochemical proton gradient) that fuels pyruvate import into the mitochondrial matrix[60,61]. Studies have shown that H_2O_2 inhibits a variety of enzymes including enzymes within the Krebs' cycle such as aconitase, alpha-ketoglutarate dehydrogenase, and Succinate Dehydrogenase[55-57, 62].

Once inhibited, the Krebs cycle can no longer supply sufficient reducing equivalents (NADH, $FADH_2$) needed to sustain the mitochondrial proton gradient. Diminished Krebs cycle supplied reducing equivalents can decrease (and eventually collapse) the mitochondrial proton gradient. This will impair the proton motive force needed for pyruvate translocase in the inner mitochondrial membrane to transport pyruvate into mitochondria in symport with a proton[60,61]. The end result is increased cytosolic pyruvate and subsequent conversion to lactate with resulting hyperlactatemia[11]. Thus, in sepsis, hyperlactatemia can be a manifestation of H_2O_2 toxicity, in which case the reduction of serum lactate alone has no effect on the outcome of sepsis[63,64].

The effect of a dysfunctional Krebs cycle on serum lactate levels can be seen with the inherited deficiency of alpha-ketoglutarate dehydrogenase, which is associated with severe congenital hyperlactatemia[65]. Under these circumstances, increasing inspired oxygen will not lower serum lactate since the problem is with the diminished supply of electrons to the electron transport chain, which collapses the proton gradient dissipating the proton motive force, and not the availability of oxygen.

Studies have shown substantial lactate production from the lungs of patients with septic shock[66]. Hypoperfusion or hypoxia is highly unlikely given that the lungs are continuously bathed in oxygen and receive the entire cardiac output. However, when combined with other studies showing decreased lung glutathione in sepsis, H_2O_2 toxicity is a strong possibility. Therapeutic removal of H_2O_2 (discussed below) can contribute to the normalization of bioenergetic function and serum lactate.

It's worth noting that the mitochondrial proton motive force fuels both ATP synthase and nicotinamide nucleotide transhydrogenase both of which are located in the inner mitochondrial membrane. The former is needed to synthesize ATP while the latter is required to generate mitochondrial NADPH, a critical source of reducing equivalents for the regeneration of mitochondrial glutathione needed to neutralize H_2O_2[13]. Thus, sepsis-associated hyperlactatemia may signal a compromised proton motive force and the start of a vicious cycle leading to increased H_2O_2 induced oxidative stress and bioenergetic failure.

Anemia

A common feature during the progression of sepsis is anemia. Several factors can contribute to the development of sepsis-associated anemia however, sepsis per se is independently associated with the development of anemia, and healthy erythrocytes exposed to plasma from sepsis patients undergo eryptosis[67,68]. H_2O_2 induced oxidative stress initiates erythrocyte suicidal cell death known as eryptosis leading to cell shrinkage and clearance from the blood[68-71]. Thus, H_2O_2 initiated eryptosis may contribute to sepsis-related anemia.

Hypocalcemia

Low serum calcium is a common finding in patients with sepsis and critical illness, with reported prevalence rates of up to 80%[72]. Hypocalcemia may be due to one or more of various causes[73]. However, during sepsis, calcium is shifted into red blood cells with significant increases in erythrocyte calcium of more than twice the control

value[74]. Given that about 85% of all cells in the body are red blood cells, this shift may significantly contribute to sepsis-associated hypocalcemia[75]. Erythrocytes exposed to oxidative stress (*i.e.*, H_2O_2) activate calcium-permeable cation channels leading to calcium entry into the cell[71]. Significantly increased lymphocyte calcium has also been reported in sepsis[76]. This suggests that the elevated blood H_2O_2 reported in sepsis may cause a more generalize intracellular shift of calcium.

Shock

Sepsis-associated hemodynamic instability can progress to septic shock, which carries a high mortality. Oxidative stress due to H_2O_2 exposure causes extensive cytoskeletal disruption to endothelial cells leading to significant endothelial retraction and microangiopathic dysfunction[22]. The net effect of microvascular H_2O_2 exposure is microangiopathic dysfunction, impaired vasomotor responsiveness, barrier disruption with edema formation, and irreversible hypotension (septic shock)[22,77]. Studies have reported hypotension in an animal model after intravenous administration of H_2O_2 [25].

Immunosuppression

Sepsis patients develop profound immunosuppression that begins within days after the onset of sepsis[7,28,30]. Lymphocytes are extremely sensitive to H_2O_2 induced apoptosis, which occurs at H_2O_2 concentrations of less than 1 μmol/L[19,20]. Studies report blood H_2O_2 concentrations in sepsis of up to 558 μmol/L, which is over 500 times the concentration of H_2O_2 needed to cause lymphocyte apoptosis[17-19]. The ability of high blood H_2O_2 concentrations to cause generalized lymphocyte apoptosis explains the profound immunosuppression observed in sepsis patients.

Respiratory failure

Sepsis-associated acute respiratory distress syndrome (ARDS) is a serious complication of sepsis that carries a high mortality. It is characterized by increased permeability of pulmonary capillary endothelial and epithelial cells. The increased vascular permeability leads to diffuse capillary leak, pulmonary edema, and eventual wet lung, which triggers the secondary development of pathological features[78,79]. Studies have demonstrated that low dose H_2O_2 can increase pulmonary vascular bed permeability and capillary filtration[80-83]. This suggests that the high levels of H_2O_2 reported in the blood of sepsis patients may have a causal role in the initiation of ARDS.

Acute kidney injury

Sepsis-associated acute kidney injury (S-AKI) is a life-threatening complication that develops in up to two-thirds of patients with sepsis or septic shock, which in half of the patients develops before seeking medical attention[84]. Once thought to be a consequence of cellular hypoxia leading to acute tubular necrosis, it is now recognized that S-AKI can occur in the setting of normal or increased renal blood flow[84]. Studies suggest a critical role for microcirculatory dysfunction, which is present in every vital organ in animal models and humans with sepsis[84-86]. When combined with studies showing a decreased substrate flux through the Krebs cycle in mice kidneys after the induction of experimental sepsis[87], these effects mirror the known toxic effects of H_2O_2, among which is microangiopathic dysfunction and Krebs cycle enzymatic inhibition[22]. In support of a role for H_2O_2 in S-AKI, studies of experimental murine sepsis employing Mito-TEMPO, a mitochondrially targeted reducing agent (antioxidant) active against H_2O_2, significantly increased renal microcirculation, glomerular filtration rate, and ATP synthesis[88,89].

The renal endothelium is highly vulnerable to oxidative stress with agents such as H_2O_2, a highly toxic oxidizing agent that can diffuse across cell membranes to impair critical signaling and regulatory function required for microvascular function[90]. Other studies report significant cytotoxicity in human tubular epithelial cells exposed to 100 μmol/L H_2O_2, while 200 μmol/L exposure caused mitochondrial cytochrome-C translocation to the cytoplasm in addition to significant intracellular increases in H_2O_2. These concentrations are within the range reported for blood H_2O_2 in sepsis patients of up to 558 μmol/L[17,91]. H_2O_2 can inhibit various enzymes involved in oxidative metabolism including Krebs cycle enzymes, ATP synthase, and nucleotide (ADP-ATP) translocase[55-57,92]. The resulting inhibition in mitochondrial oxidative flux may contribute to the increased glycolytic production of lactate by proximal tubule cells observed during sepsis[93]. Increased glycolysis would revert to oxidative phosphorylation when H_2O_2 induced inhibition of mitochondrial oxidative metabolism

is resolved. Lastly, rat renal artery infusion of 70 mmol/L H_2O_2 (140x that found in human sepsis blood) is reported to cause massive proteinuria without electron microscopic ultrastructural glomerular abnormalities[94]. This is consistent with the minimal postmortem histological findings in human S-AKI[84,86]. This suggests that renal exposure to blood H_2O_2 levels observed in human sepsis may cause cellular dysfunction without overt signs of cellular damage.

Coagulopathy

Disseminated intravascular coagulation (DIC) is a life-threatening complication frequently encountered in sepsis that is characterized by the systemic activation of the coagulation system leading to microvascular thrombosis, and potentially life-threatening hemorrhage due to consumption of platelets and coagulation factors[95]. DIC can originate from damage to the microvasculature, which triggers the extrinsic coagulation cascade[96]. H_2O_2 can cause microvascular injury by peroxidation of endothelial cell membranes, which triggers the expression of tissue factor and subsequent systemic activation of the extrinsic coagulation pathway leading to DIC [97-99]. Intravenous administration of H_2O_2 is reported to have resulted in fatal sepsis and DIC, underscoring the role of H_2O_2 induced oxidative stress in both of these conditions[100].

On a more fundamental level, the endothelium is critically involved in preventing inappropriate coagulation by maintaining barrier function and producing several endogenous anticoagulants[101]. The elevated levels of blood H_2O_2 reported in sepsis can permeate endothelial cells throughout the body causing substantial oxidative stress accompanied by profound disruption in both form and function[77,102]. Studies have reported significant endothelial dysfunction that is associated with mortality and severity of coagulopathy[101]. H_2O_2 induced endothelial dysfunction can explain why anticoagulants fail to show a survival benefit in sepsis-induced DIC[103] since these agents fail to restore endothelial redox homeostasis.

Encephalopathy

Sepsis-associated encephalopathy (SAE) is a diffuse cerebral dysfunction ranging from lethargy and lack of concentration to personality changes, delirium, and coma that occurs secondary to sepsis in the absence of direct central nervous system (CNS) infection. SAE affects up to 70% of sepsis patients and is associated with higher mortality and poorer long term outcomes with half of surviving patients suffering from long-term cognitive defects[104,105]. The brain is highly sensitive to H_2O_2 induced oxidative damage and dysfunction, and studies report dose-dependent cytotoxicity starting at H_2O_2 exposures of 10 μmol/L[106]. Encephalopathy is reported to occur after the accidental ingestion of H_2O_2[107]. Encephalopathy was also reported after intravenous administration of H_2O_2 for alternative medicine therapy[100].

H_2O_2 is diffusible through cell membranes which facilitates its diffusion into the central nervous system where it can disrupt neuronal and synaptic function. Studies have shown that H_2O_2 can alter neuron membrane properties and impair synaptic transmission leading to hyperexcitability and epileptiform activity[108,109]. This is notable because epileptic seizures can be a manifestation of SAE. Other studies have demonstrated bioenergetic impairment with decreased ATP biosynthesis and utilization in neurons exposed to H_2O_2[110,111]. H_2O_2 has also been reported to alter rat hippocampal synaptic plasticity, which can negatively impact long-term potentiation, learning, and memory[112]. Thus, the presence of elevated levels of blood H_2O_2 in sepsis can have acute and chronic effects on brain function and cognition.

TREATMENT

Sepsis is a life-threatening medical emergency that can precipitously evolve into hemodynamic instability, septic shock, and death. Thus it may not be possible or prudent to wait for a blood H_2O_2 level if clinical signs of H_2O_2 toxicity are present. Additionally, it takes some time before free H_2O_2 can accumulate in the bloodstream given the multiple layers of reductive (antioxidant) defense systems that mitochondrial H_2O_2 must traverse on its way to the intravascular compartment including mitochondrial and cytoplasmic glutathione followed by interstitial albumin whose cys34 amino acid can react with H_2O_2 (60% of total albumin) and ultimately serum albumin (40% of total albumin) and red blood cell reductive (glutathione) capacity [13]. During the time it takes to reach the blood stream and build-up, toxic levels of

intracellular H_2O_2 can inhibit critical cellular bioenergetic reactions leading to compromised bioenergetic function. This was demonstrated in ulcerative colitis, an inflammatory bowel disease, in which a primary increase in colonic epithelial H_2O_2, thought to have a causal role in this disease, resulted in impaired beta-oxidation due to H_2O_2 inhibition of mitochondrial thiolase, the last enzyme in the beta-oxidation cascade[113].

Within this context, the data support the critical need for reduction of systemic H_2O_2 in sepsis to prevent bioenergetic organ failure and restore microcirculatory function. Restoration of redox homeostasis by the elimination of excess H_2O_2 must accompany other therapeutic interventions to optimize clinical responsiveness and outcome. Sodium thiosulfate (STS) is a direct-acting reducing agent that can neutralize H_2O_2 upon contact.

STS is approved for use in cyanide poisoning with a recommended dose of 12.5 g over slow IV infusion (10 to 20 min) in adults and 250 mg/kg in children[114]. Similar dosing regimens can be considered in sepsis. Repeat dosing can be guided by clinical status, blood reducing capacity (glutathione, plasma thiols), and blood H_2O_2 levels. The general chemical reaction for the reduction of H_2O_2 with sodium thiosulfate yields sodium trithionate, sodium sulfate, and water[115].

$2Na_2S_2O_3 + 4H_2O_2 \rightarrow Na_2S_3O_6 + Na_2SO_4 + 4H_2O$

The rationale underlying STS administration in sepsis is to reduce blood H_2O_2 to normal (less than 30 μmol/L) in order to allow intracellular H_2O_2 to diffuse down its concentration gradient into the systemic circulation where it can be neutralized by STS. STS is generally well tolerated and is an accepted therapy for cisplatin toxicity and renal failure associated calciphylaxis (25 g three times weekly)[116,117]. High dose STS (up to 16 g per M^2 surface area, repeated after 4 h) is reported to be well tolerated in children under 12 years of age[118].

STS is reported to replenish intracellular glutathione, which will aid in the removal of intracellular H_2O_2 and restoration of redox homeostasis[119,120]. Decreasing serum lactate indicates that H_2O_2-induced Krebs cycle inhibition and bioenergetic dysfunction are being reversed. Restoration of vascular responsiveness by STS may cause extant vasopressor measures to have an unanticipated amplified effect. Thus, STS administration in critically ill patients should be accompanied by close patient monitoring. Finally, if STS therapy proves to be successful in the treatment of sepsis then treatment with STS should be considered in all critically ill (hypermetabolic) patients in order to restore depleted systemic reducing equivalents before blood H_2O_2 becomes toxically elevated.

Specific treatment considerations

ARDS: Inhaled STS may have a beneficial effect to neutralize H_2O_2 that has diffused through the alveolar-capillary membrane causing oxidant damage in the alveolar space.

S-AKI: Primary prevention of S-AKI is not possible in all patients because most patients developing S-AKI already have it at presentation. Administration of STS should be considered when patients first seek medical care to initiate primary or secondary prevention.

The evidence supports the use of STS as a specific therapeutic agent for the treatment of sepsis and its associated complications. Given the high mortality, significant societal burden, and absence of a safe and effective treatment for this deadly condition, clinical studies are urgently needed to determine the effectiveness of STS for the treatment of sepsis.

CONCLUSION

The mortality in sepsis is unacceptably high because there is no specific therapy to treat the sepsis syndrome. H_2O_2 toxicity mirrors the clinical and laboratory abnormalities observed in sepsis, and toxic levels of blood H_2O_2 have been reported in this condition. This and other data implicate H_2O_2 as the causal factor in the pathogenesis of sepsis, which predictably develops accompanied by systemic depletion of reducing equivalents (*i.e.*, glutathione) needed for the reduction (neutralization) of metabolically generated H_2O_2. Once the body's reductive (antioxidant) capacity is depleted, H_2O_2 will continue to be generated and flood the system.

Prolonged supraphysiological production of H_2O_2 generated by electron transport chain hyperactivity during a hypermetabolic state (such as sepsis) can overwhelm

cellular reductive systems leading to H_2O_2 accumulation within tissues and blood. H_2O_2 is a highly toxic membrane-permeable metabolic poison that can cause severe bioenergetic dysfunction and cellular damage if allowed to accumulate. Continued exposure can lead to the collapse of systemic redox homeostasis, proton motive force dissipation, organ failure, microvascular dysfunction, and fatal septic shock. Reduction of blood H_2O_2 is paramount in order to prevent H_2O_2 toxicity from irreversibly shutting down cellular metabolism.

The data support the use of sodium thiosulfate as a systemic reducing agent with the goal of restoring redox homeostasis by neutralizing excess systemic H_2O_2. Prophylactic use of sodium thiosulfate in all critically ill (hypermetabolic) patients should be considered before irreversible H_2O_2 induced bioenergetic failure and microvascular dysfunction develop.

Based on the data, the missing critical intervention to improve patient outcomes and reduce mortality in patients with sepsis and septic shock is the normalization of systemic redox homeostasis. The addition of specialists in redox medicine to the team providing care to critically ill patients can contribute to achieving this heretofore elusive goal.

REFERENCES

1 **Rudd KE**, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; **395**: 200-211 [PMID: 31954465 DOI: 10.1016/S0140-6736(19)32989-7]

2 **Klein Klouwenberg PM**, Cremer OL, van Vught LA, Ong DS, Frencken JF, Schultz MJ, Bonten MJ, van der Poll T. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. *Crit Care* 2015; **19**: 319 [PMID: 26346055 DOI: 10.1186/s13054-015-1035-1]

3 **Lin GL**, McGinley JP, Drysdale SB, Pollard AJ. Epidemiology and Immune Pathogenesis of Viral Sepsis. *Front Immunol* 2018; **9**: 2147 [PMID: 30319615 DOI: 10.3389/fimmu.2018.02147]

4 **Nagar H**, Piao S, Kim CS. Role of Mitochondrial Oxidative Stress in Sepsis. *Acute Crit Care* 2018; **33**: 65-72 [PMID: 31723865 DOI: 10.4266/acc.2018.00157]

5 **Phua J**, Ngerng W, See K, Tay C, Kiong T, Lim H, Chew M, Yip H, Tan A, Khalizah H, Capistrano R, Lee K, Mukhopadhyay A. Characteristics and outcomes of culture-negative *vs* culture-positive severe sepsis. *Crit Care* 2013; **17**: R202 [PMID: 24028771 DOI: 10.1186/cc12896]

6 **Molina F**, Castaño P, Plaza M, Hincapié C, Maya W, Cataño JC, González J, León A, Jaimes F. Positive Culture and Prognosis in Patients With Sepsis: A Prospective Cohort Study. *J Intensive Care Med* 2020; **35**: 755-762 [PMID: 29925284 DOI: 10.1177/0885066618783656]

7 **Venet F**, Rimmelé T, Monneret G. Management of Sepsis-Induced Immunosuppression. *Crit Care Clin* 2018; **34**: 97-106 [PMID: 29149944 DOI: 10.1016/j.ccc.2017.08.007]

8 **Boekstegers P**, Weidenhöfer S, Kapsner T, Werdan K. Skeletal muscle partial pressure of oxygen in patients with sepsis. *Crit Care Med* 1994; **22**: 640-650 [PMID: 8143474 DOI: 10.1097/00003246-199404000-00021]

9 **Fink MP**. Cytopathic hypoxia. Mitochondrial dysfunction as mechanism contributing to organ dysfunction in sepsis. *Crit Care Clin* 2001; **17**: 219-237 [PMID: 11219231 DOI: 10.1016/s0749-0704(05)70161-5]

10 **Supinski GS**, Schroder EA, Callahan LA. Mitochondria and Critical Illness. *Chest* 2020; **157**: 310-322 [PMID: 31494084 DOI: 10.1016/j.chest.2019.08.2182]

11 **Garcia-Alvarez M**, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. *Crit Care* 2014; **18**: 503 [PMID: 25394679 DOI: 10.1186/s13054-014-0503-3]

12 **Lee SG**, Song J, Park DW, Moon S, Cho HJ, Kim JY, Park J, Cha JH. Prognostic value of lactate levels and lactate clearance in sepsis and septic shock with initial hyperlactatemia: A retrospective cohort study according to the Sepsis-3 definitions. *Medicine (Baltimore)* 2021; **100**: e24835 [PMID: 33607851 DOI: 10.1097/MD.0000000000024835]

13 **Mailloux RJ**. Mitochondrial Antioxidants and the Maintenance of Cellular Hydrogen Peroxide Levels. *Oxid Med Cell Longev* 2018; **2018**: 7857251 [PMID: 30057684 DOI: 10.1155/2018/7857251]

14 **Liu SS**. Generating, partitioning, targeting and functioning of superoxide in mitochondria. *Biosci Rep* 1997; **17**: 259-272 [PMID: 9337481 DOI: 10.1023/a:1027328510931]

15 **Turrens JF**. Superoxide production by the mitochondrial respiratory chain. *Biosci Rep* 1997; **17**: 3-8 [PMID: 9171915 DOI: 10.1023/a:1027374931887]

16 **Nolfi-Donegan D**, Braganza A, Shiva S. Mitochondrial electron transport chain: Oxidative phosphorylation, oxidant production, and methods of measurement. *Redox Biol* 2020; **37**: 101674 [PMID: 32811789 DOI: 10.1016/j.redox.2020.101674]

17 **19 van Asbeck BS**, Braams R, Aarsman JM, Sprong RC, Groenewegen A. Hydrogen Peroxide In Blood Of Patients With Sepsis Syndrome: A Realistic Phenomenon. *Crit Care Med* 1995; 23: A169 [DOI: 10.1097/00003246-199501001-00290]

18 **Forman HJ**, Bernardo A, Davies KJ. What is the concentration of hydrogen peroxide in blood and plasma? *Arch Biochem Biophys* 2016; **603**: 48-53 [PMID: 27173735 DOI: 10.1016/j.abb.2016.05.005]

19 **Halliwell B**, Clement MV, Long LH. Hydrogen peroxide in the human body. *FEBS Lett* 2000; **486**: 10-13 [PMID: 11108833 DOI: 10.1016/s0014-5793(00)02197-9]

20 **Antunes F**, Cadenas E. Cellular titration of apoptosis with steady state concentrations of H(2)O(2): submicromolar levels of H(2)O(2) induce apoptosis through Fenton chemistry independent of the cellular thiol state. *Free Radic Biol Med* 2001; **30**: 1008-1018 [PMID: 11316581 DOI: 10.1016/s0891-5849(01)00493-2]

21 **Chandel NS**. Mitochondria as signaling organelles. *BMC Biol* 2014; **12**: 34 [PMID: 24884669 DOI: 10.1186/1741-7007-12-34]

22 **Pravda J**. Metabolic theory of septic shock. *World J Crit Care Med* 2014; **3**: 45-54 [PMID: 24892019 DOI: 10.5492/wjccm.v3.i2.45]

23 **Evans T**, Jin H, Elkins N, Shapiro JI. Effect of acidosis on hydrogen peroxide injury to the isolated perfused rat heart. *Am J Physiol* 1995; **269**: H308-H312 [PMID: 7631862 DOI: 10.1152/ajpheart.1995.269.1.H308]

24 **Ballinger SW**, Van Houten B, Jin GF, Conklin CA, Godley BF. Hydrogen peroxide causes significant mitochondrial DNA damage in human RPE cells. *Exp Eye Res* 1999; **68**: 765-772 [PMID: 10375440 DOI: 10.1006/exer.1998.0661]

25 **Shenep JL**, Stokes DC, Hughes WT. Lack of antibacterial activity after intravenous hydrogen peroxide infusion in experimental Escherichia coli sepsis. *Infect Immun* 1985; **48**: 607-610 [PMID: 3888840 DOI: 10.1128/IAI.48.3.607-610.1985]

26 **Weiss SJ**. Neutrophil-mediated methemoglobin formation in the erythrocyte. The role of superoxide and hydrogen peroxide. *J Biol Chem* 1982; **257**: 2947-2953 [PMID: 6277918]

27 **McBride MA**, Patil TK, Bohannon JK, Hernandez A, Sherwood ER, Patil NK. Immune Checkpoints: Novel Therapeutic Targets to Attenuate Sepsis-Induced Immunosuppression. *Front Immunol* 2020; **11**: 624272 [PMID: 33613563 DOI: 10.3389/fimmu.2020.624272]

28 **Ono S**, Tsujimoto H, Hiraki S, Aosasa S. Mechanisms of sepsis-induced immunosuppression and immunological modification therapies for sepsis. *Ann Gastroenterol Surg* 2018; **2**: 351-358 [PMID: 30238076 DOI: 10.1002/ags3.12194]

29 **Reddy RC**, Chen GH, Tekchandani PK, Standiford TJ. Sepsis-induced immunosuppression: from bad to worse. *Immunol Res* 2001; **24**: 273-287 [PMID: 11817325 DOI: 10.1385/IR:24:3:273]

30 **Boomer JS**, To K, Chang KC, Takasu O, Osborne DF, Walton AH, Bricker TL, Jarman SD 2nd, Kreisel D, Krupnick AS, Srivastava A, Swanson PE, Green JM, Hotchkiss RS. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA* 2011; **306**: 2594-2605 [PMID: 22187279 DOI: 10.1001/jama.2011.1829]

31 **Ayar G**, Sahin S, Men Atmaca Y, Uysal Yazici M, Neselioglu S, Erel O. Thiol-disulphide homeostasis is an oxidative stress indicator in critically ill children with sepsis. *Arch Argent Pediatr* 2019; **117**: 143-148 [PMID: 31063297 DOI: 10.5546/aap.2019.eng.143]

32 **Turell L**, Radi R, Alvarez B. The thiol pool in human plasma: the central contribution of albumin to redox processes. *Free Radic Biol Med* 2013; **65**: 244-253 [PMID: 23747983 DOI: 10.1016/j.freeradbiomed.2013.05.050]

33 **Gerencser AA**, Chinopoulos C, Birket MJ, Jastroch M, Vitelli C, Nicholls DG, Brand MD. Quantitative measurement of mitochondrial membrane potential in cultured cells: calcium-induced de- and hyperpolarization of neuronal mitochondria. *J Physiol* 2012; **590**: 2845-2871 [PMID: 22495585 DOI: 10.1113/jphysiol.2012.228387]

34 **Aon MA**, Stanley BA, Sivakumaran V, Kembro JM, O'Rourke B, Paolocci N, Cortassa S. Glutathione/thioredoxin systems modulate mitochondrial H2O2 emission: an experimental-computational study. *J Gen Physiol* 2012; **139**: 479-491 [PMID: 22585969 DOI: 10.1085/jgp.201210772]

35 **Ribas V**, García-Ruiz C, Fernández-Checa JC. Glutathione and mitochondria. *Front Pharmacol* 2014; **5**: 151 [PMID: 25024695 DOI: 10.3389/fphar.2014.00151]

36 **Lu SC**. Glutathione synthesis. *Biochim Biophys Acta* 2013; **1830**: 3143-3153 [PMID: 22995213 DOI: 10.1016/j.bbagen.2012.09.008]

37 **Tang X**, Luo YX, Chen HZ, Liu DP. Mitochondria, endothelial cell function, and vascular diseases. *Front Physiol* 2014; **5**: 175 [PMID: 24834056 DOI: 10.3389/fphys.2014.00175]

38 **Stowe DF**, Camara AK. Mitochondrial reactive oxygen species production in excitable cells: modulators of mitochondrial and cell function. *Antioxid Redox Signal* 2009; **11**: 1373-1414 [PMID: 19187004 DOI: 10.1089/ars.2008.2331]

39 **Muyderman H**, Nilsson M, Sims NR. Highly selective and prolonged depletion of mitochondrial glutathione in astrocytes markedly increases sensitivity to peroxynitrite. *J Neurosci* 2004; **24**: 8019-8028 [PMID: 15371502 DOI: 10.1523/JNEUROSCI.1103-04.2004]

40 **Marí M**, de Gregorio E, de Dios C, Roca-Agujetas V, Cucarull B, Tutusaus A, Morales A, Colell A. Mitochondrial Glutathione: Recent Insights and Role in Disease. *Antioxidants (Basel)* 2020; **9** [PMID: 32987701 DOI: 10.3390/antiox9100909]

41 **Zorov DB**, Juhaszova M, Sollott SJ. Mitochondrial ROS-induced ROS release: an update and

review. *Biochim Biophys Acta* 2006; **1757**: 509-517 [PMID: 16829228 DOI: 10.1016/j.bbabio.2006.04.029]

42 **Jeschke MG**, Gauglitz GG, Kulp GA, Finnerty CC, Williams FN, Kraft R, Suman OE, Mlcak RP, Herndon DN. Long-term persistance of the pathophysiologic response to severe burn injury. *PLoS One* 2011; **6**: e21245 [PMID: 21789167 DOI: 10.1371/journal.pone.0021245]

43 **Efron PA**, Mohr AM, Bihorac A, Horiguchi H, Hollen MK, Segal MS, Baker HV, Leeuwenburgh C, Moldawer LL, Moore FA, Brakenridge SC. Persistent inflammation, immunosuppression, and catabolism and the development of chronic critical illness after surgery. *Surgery* 2018; **164**: 178-184 [PMID: 29807651 DOI: 10.1016/j.surg.2018.04.011]

44 **Cox MC**, Brakenridge SC, Stortz JA, Hawkins RB, Darden DB, Ghita GL, Mohr AM, Moldawer LL, Efron PA, Moore FA. Abdominal sepsis patients have a high incidence of chronic critical illness with dismal long-term outcomes. *Am J Surg* 2020; **220**: 1467-1474 [PMID: 32807383 DOI: 10.1016/j.amjsurg.2020.07.016]

45 **Stortz JA**, Mira JC, Raymond SL, Loftus TJ, Ozrazgat-Baslanti T, Wang Z, Ghita GL, Leeuwenburgh C, Segal MS, Bihorac A, Brumback BA, Mohr AM, Efron PA, Moldawer LL, Moore FA, Brakenridge SC. Benchmarking clinical outcomes and the immunocatabolic phenotype of chronic critical illness after sepsis in surgical intensive care unit patients. *J Trauma Acute Care Surg* 2018; **84**: 342-349 [PMID: 29251709 DOI: 10.1097/TA.0000000000001758]

46 **Kalghatgi S**, Spina CS, Costello JC, Liesa M, Morones-Ramirez JR, Slomovic S, Molina A, Shirihai OS, Collins JJ. Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in Mammalian cells. *Sci Transl Med* 2013; **5**: 192ra85 [PMID: 23825301 DOI: 10.1126/scitranslmed.3006055]

47 **Wallace DC**. Mitochondrial diseases in man and mouse. *Science* 1999; **283**: 1482-1488 [PMID: 10066162 DOI: 10.1126/science.283.5407.1482]

48 **Taylor RW**, Turnbull DM. Mitochondrial DNA mutations in human disease. *Nat Rev Genet* 2005; **6**: 389-402 [PMID: 15861210 DOI: 10.1038/nrg1606]

49 **Ricci C**, Pastukh V, Leonard J, Turrens J, Wilson G, Schaffer D, Schaffer SW. Mitochondrial DNA damage triggers mitochondrial-superoxide generation and apoptosis. *Am J Physiol Cell Physiol* 2008; **294**: C413-C422 [PMID: 18077603 DOI: 10.1152/ajpcell.00362.2007]

50 **Canter JA**, Eshaghian A, Fessel J, Summar ML, Roberts LJ, Morrow JD, Sligh JE, Haines JL. Degree of heteroplasmy reflects oxidant damage in a large family with the mitochondrial DNA A8344G mutation. *Free Radic Biol Med* 2005; **38**: 678-683 [PMID: 15683723 DOI: 10.1016/j.freeradbiomed.2004.11.031]

51 **Rose G**, Passarino G, Scornaienchi V, Romeo G, Dato S, Bellizzi D, Mari V, Feraco E, Maletta R, Bruni A, Franceschi C, De Benedictis G. The mitochondrial DNA control region shows genetically correlated levels of heteroplasmy in leukocytes of centenarians and their offspring. *BMC Genomics* 2007; **8**: 293 [PMID: 17727699 DOI: 10.1186/1471-2164-8-293]

52 **Lee HC**, Wei YH. Oxidative stress, mitochondrial DNA mutation, and apoptosis in aging. *Exp Biol Med (Maywood)* 2007; **232**: 592-606 [PMID: 17463155]

53 **Jinich A**, Flamholz A, Ren H, Kim SJ, Sanchez-Lengeling B, Cotton CAR, Noor E, Aspuru-Guzik A, Bar-Even A. Quantum chemistry reveals thermodynamic principles of redox biochemistry. *PLoS Comput Biol* 2018; **14**: e1006471 [PMID: 30356318 DOI: 10.1371/journal.pcbi.1006471]

54 **Viola HM**, Hool LC. Qo site of mitochondrial complex III is the source of increased superoxide after transient exposure to hydrogen peroxide. *J Mol Cell Cardiol* 2010; **49**: 875-885 [PMID: 20688078 DOI: 10.1016/j.yjmcc.2010.07.015]

55 **Tretter L**, Adam-Vizi V. Inhibition of Krebs cycle enzymes by hydrogen peroxide: A key role of [alpha]-ketoglutarate dehydrogenase in limiting NADH production under oxidative stress. *J Neurosci* 2000; **20**: 8972-8979 [PMID: 11124972 DOI: 10.1523/JNEUROSCI.20-24-08972.2000]

56 **Tretter L**, Adam-Vizi V. Alpha-ketoglutarate dehydrogenase: a target and generator of oxidative stress. *Philos Trans R Soc Lond B Biol Sci* 2005; **360**: 2335-2345 [PMID: 16321804 DOI: 10.1098/rstb.2005.1764]

57 **Nulton-Persson AC**, Szweda LI. Modulation of mitochondrial function by hydrogen peroxide. *J Biol Chem* 2001; **276**: 23357-23361 [PMID: 11283020 DOI: 10.1074/jbc.M100320200]

58 **Levy RJ**. Mitochondrial dysfunction, bioenergetic impairment, and metabolic down-regulation in sepsis. *Shock* 2007; **28**: 24-28 [PMID: 17483747 DOI: 10.1097/01.shk.0000235089.30550.2d]

59 **Japiassú AM**, Santiago AP, d'Avila JC, Garcia-Souza LF, Galina A, Castro Faria-Neto HC, Bozza FA, Oliveira MF. Bioenergetic failure of human peripheral blood monocytes in patients with septic shock is mediated by reduced F1Fo adenosine-5'-triphosphate synthase activity. *Crit Care Med* 2011; **39**: 1056-1063 [PMID: 21336129 DOI: 10.1097/CCM.0b013e31820eda5c]

60 **Bender T**, Martinou JC. The mitochondrial pyruvate carrier in health and disease: To carry or not to carry? *Biochim Biophys Acta* 2016; **1863**: 2436-2442 [PMID: 26826034 DOI: 10.1016/j.bbamcr.2016.01.017]

61 **Zangari J**, Petrelli F, Maillot B, Martinou JC. The Multifaceted Pyruvate Metabolism: Role of the Mitochondrial Pyruvate Carrier. *Biomolecules* 2020; **10** [PMID: 32708919 DOI: 10.3390/biom10071068]

62 **Knaus UG**. Oxidants in Physiological Processes. *Handb Exp Pharmacol* 2021; **264**: 27-47 [PMID: 32767144 DOI: 10.1007/164_2020_380]

63 **Stacpoole PW**, Harman EM, Curry SH, Baumgartner TG, Misbin RI. Treatment of lactic acidosis with dichloroacetate. *N Engl J Med* 1983; **309**: 390-396 [PMID: 6877297 DOI:

10.1056/NEJM198308183090702]
64 **Stacpoole PW**, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, Duncan CA, Harman EM, Henderson GN, Jenkinson S. A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. *N Engl J Med* 1992; **327**: 1564-1569 [PMID: 1435883 DOI: 10.1056/NEJM199211263272204]
65 **Bonnefont JP**, Chretien D, Rustin P, Robinson B, Vassault A, Aupetit J, Charpentier C, Rabier D, Saudubray JM, Munnich A. Alpha-ketoglutarate dehydrogenase deficiency presenting as congenital lactic acidosis. *J Pediatr* 1992; **121**: 255-258 [PMID: 1640293 DOI: 10.1016/s0022-3476(05)81199-0]
66 **Opdam H**, Bellomo R. Oxygen consumption and lactate release by the lung after cardiopulmonary bypass and during septic shock. *Crit Care Resusc* 2000; **2**: 181-187 [PMID: 16599894]
67 **Jansma G**, de Lange F, Kingma WP, Vellinga NA, Koopmans M, Kuiper MA, Boerma EC. 'Sepsis-related anemia' is absent at hospital presentation; a retrospective cohort analysis. *BMC Anesthesiol* 2015; **15**: 55 [PMID: 25947889 DOI: 10.1186/s12871-015-0035-7]
68 **Kempe DS**, Akel A, Lang PA, Hermle T, Biswas R, Muresanu J, Friedrich B, Dreischer P, Wolz C, Schumacher U, Peschel A, Götz F, Döring G, Wieder T, Gulbins E, Lang F. Suicidal erythrocyte death in sepsis. *J Mol Med (Berl)* 2007; **85**: 273-281 [PMID: 17180345 DOI: 10.1007/s00109-006-0123-8]
69 **Sun Y**, Liu G, Jiang Y, Wang H, Xiao H, Guan G. Erythropoietin Protects Erythrocytes Against Oxidative Stress-Induced Eryptosis In Vitro. *Clin Lab* 2018; **64**: 365-369 [PMID: 29739123 DOI: 10.7754/Clin.Lab.2017.170924]
70 **Repsold L**, Joubert AM. Eryptosis: An Erythrocyte's Suicidal Type of Cell Death. *Biomed Res Int* 2018; **2018**: 9405617 [PMID: 29516014 DOI: 10.1155/2018/9405617]
71 **Bissinger R**, Bhuyan AAM, Qadri SM, Lang F. Oxidative stress, eryptosis and anemia: a pivotal mechanistic nexus in systemic diseases. *FEBS J* 2019; **286**: 826-854 [PMID: 30028073 DOI: 10.1111/febs.14606]
72 **Steele T**, Kolamunnage-Dona R, Downey C, Toh CH, Welters I. Assessment and clinical course of hypocalcemia in critical illness. *Crit Care* 2013; **17**: R106 [PMID: 23734769 DOI: 10.1186/cc12756]
73 **Tinawi M**. Disorders of Calcium Metabolism: Hypocalcemia and Hypercalcemia. *Cureus* 2021; **13**: e12420 [PMID: 33542868 DOI: 10.7759/cureus.12420]
74 **Todd JC 3rd**, Mollitt DL. Effect of sepsis on erythrocyte intracellular calcium homeostasis. *Crit Care Med* 1995; **23**: 459-465 [PMID: 7874895 DOI: 10.1097/00003246-199503000-00008]
75 **Rogers S**, Doctor A. Red Blood Cell Dysfunction in Critical Illness. *Crit Care Clin* 2020; **36**: 267-292 [PMID: 32172813 DOI: 10.1016/j.ccc.2019.12.008]
76 **Zaloga GP**, Washburn D, Black KW, Prielipp R. Human sepsis increases lymphocyte intracellular calcium. *Crit Care Med* 1993; **21**: 196-202 [PMID: 8428469 DOI: 10.1097/00003246-199302000-00009]
77 **Joffre J**, Hellman J. Oxidative Stress and Endothelial Dysfunction in Sepsis and Acute Inflammation. *Antioxid Redox Signal* 2021 [PMID: 33637016 DOI: 10.1089/ars.2021.0027]
78 **Cardinal-Fernández P**, Lorente JA, Ballén-Barragán A, Matute-Bello G. Acute Respiratory Distress Syndrome and Diffuse Alveolar Damage. New Insights on a Complex Relationship. *Ann Am Thorac Soc* 2017; **14**: 844-850 [PMID: 28570160 DOI: 10.1513/AnnalsATS.201609-728PS]
79 **Sharp C**, Millar AB, Medford AR. Advances in understanding of the pathogenesis of acute respiratory distress syndrome. *Respiration* 2015; **89**: 420-434 [PMID: 25925331 DOI: 10.1159/000381102]
80 **Habib MP**, Clements NC. Effects of low-dose hydrogen peroxide in the isolated perfused rat lung. *Exp Lung Res* 1995; **21**: 95-112 [PMID: 7729381 DOI: 10.3109/01902149509031747]
81 **Seeger W**, Hansen T, Rössig R, Schmehl T, Schütte H, Krämer HJ, Walmrath D, Weissmann N, Grimminger F, Suttorp N. Hydrogen peroxide-induced increase in lung endothelial and epithelial permeability--effect of adenylate cyclase stimulation and phosphodiesterase inhibition. *Microvasc Res* 1995; **50**: 1-17 [PMID: 7476570 DOI: 10.1006/mvre.1995.1033]
82 **Zhou X**, Qian Y, Yuan D, Feng Q, He P. H_2O_2 -induced microvessel barrier dysfunction: the interplay between reactive oxygen species, nitric oxide, and peroxynitrite. *Physiol Rep* 2019; **7** [PMID: 31448579 DOI: 10.14814/phy2.14206]
83 **He P**, Talukder MAH, Gao F. Oxidative Stress and Microvessel Barrier Dysfunction. *Front Physiol* 2020; **11**: 472 [PMID: 32536875 DOI: 10.3389/fphys.2020.00472]
84 **Manrique-Caballero CL**, Del Rio-Pertuz G, Gomez H. Sepsis-Associated Acute Kidney Injury. *Crit Care Clin* 2021; **37**: 279-301 [PMID: 33752856 DOI: 10.1016/j.ccc.2020.11.010]
85 **Post EH**, Kellum JA, Bellomo R, Vincent JL. Renal perfusion in sepsis: from macro- to microcirculation. *Kidney Int* 2017; **91**: 45-60 [PMID: 27692561 DOI: 10.1016/j.kint.2016.07.032]
86 **Peerapornratana S**, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 2019; **96**: 1083-1099 [PMID: 31443997 DOI: 10.1016/j.kint.2019.05.026]
87 **Waltz P**, Carchman E, Gomez H, Zuckerbraun B. Sepsis results in an altered renal metabolic and osmolyte profile. *J Surg Res* 2016; **202**: 8-12 [PMID: 27083942 DOI: 10.1016/j.jss.2015.12.011]
88 **Patil NK**, Parajuli N, MacMillan-Crow LA, Mayeux PR. Inactivation of renal mitochondrial respiratory complexes and manganese superoxide dismutase during sepsis: mitochondria-targeted antioxidant mitigates injury. *Am J Physiol Renal Physiol* 2014; **306**: F734-F743 [PMID: 24500690

DOI: 10.1152/ajprenal.00643.2013]
89 **McCarthy C**, Kenny LC. Therapeutically targeting mitochondrial redox signalling alleviates endothelial dysfunction in preeclampsia. *Sci Rep* 2016; **6**: 32683 [PMID: 27604418 DOI: 10.1038/srep32683]
90 **Ratliff BB**, Abdulmahdi W, Pawar R, Wolin MS. Oxidant Mechanisms in Renal Injury and Disease. *Antioxid Redox Signal* 2016; **25**: 119-146 [PMID: 26906267 DOI: 10.1089/ars.2016.6665]
91 **Cao Y**, Xu J, Cui D, Liu L, Zhang S, Shen B, Wu Y, Zhang Q. Protective effect of carnosine on hydrogen peroxide-induced oxidative stress in human kidney tubular epithelial cells. *Biochem Biophys Res Commun* 2021; **534**: 576-582 [PMID: 33276949 DOI: 10.1016/j.bbrc.2020.11.037]
92 **Tatsumi T**, Kako KJ. Effects of hydrogen peroxide on mitochondrial enzyme function studied in situ in rat heart myocytes. *Basic Res Cardiol* 1993; **88**: 199-211 [PMID: 8216172 DOI: 10.1007/BF00794993]
93 **Sun J**, Zhang J, Tian J, Virzì GM, Digvijay K, Cueto L, Yin Y, Rosner MH, Ronco C. Mitochondria in Sepsis-Induced AKI. *J Am Soc Nephrol* 2019; **30**: 1151-1161 [PMID: 31076465 DOI: 10.1681/ASN.2018111126]
94 **Yoshioka T**, Ichikawa I, Fogo A. Reactive oxygen metabolites cause massive, reversible proteinuria and glomerular sieving defect without apparent ultrastructural abnormality. *J Am Soc Nephrol* 1991; **2**: 902-912 [PMID: 1721553]
95 **Adelborg K**, Larsen JB, Hvas AM. Disseminated intravascular coagulation: epidemiology, biomarkers, and management. *Br J Haematol* 2021; **192**: 803-818 [PMID: 33555051 DOI: 10.1111/bjh.17172]
96 **Iba T**, Umemura Y, Watanabe E, Wada T, Hayashida K, Kushimoto S; Japanese Surviving Sepsis Campaign Guideline Working Group for disseminated intravascular coagulation. Diagnosis of sepsis-induced disseminated intravascular coagulation and coagulopathy. *Acute Med Surg* 2019; **6**: 223-232 [PMID: 31304023 DOI: 10.1002/ams2.411]
97 **Ambrosio G**, Tritto I, Golino P. Reactive oxygen metabolites and arterial thrombosis. *Cardiovasc Res* 1997; **34**: 445-452 [PMID: 9231027 DOI: 10.1016/s0008-6363(97)00101-6]
98 **Penn MS**, Patel CV, Cui MZ, DiCorleto PE, Chisolm GM. LDL increases inactive tissue factor on vascular smooth muscle cell surfaces: hydrogen peroxide activates latent cell surface tissue factor. *Circulation* 1999; **99**: 1753-1759 [PMID: 10190887 DOI: 10.1161/01.cir.99.13.1753]
99 **van Vught LA**, Uhel F, Ding C, Van't Veer C, Scicluna BP, Peters-Sengers H, Klein Klouwenberg PMC, Nürnberg P, Cremer OL, Schultz MJ, van der Poll T; MARS consortium. Consumptive coagulopathy is associated with a disturbed host response in patients with sepsis. *J Thromb Haemost* 2021; **19**: 1049-1063 [PMID: 33492719 DOI: 10.1111/jth.15246]
100 **Wetter DA**, Davis MD. Ulceration of the arm attributed to a spider bite and treated with intravenous hydrogen peroxide: a cautionary tale. *Arch Dermatol* 2006; **142**: 1658-1659 [PMID: 17179007 DOI: 10.1001/archderm.142.12.1658]
101 **Walborn A**, Rondina M, Mosier M, Fareed J, Hoppensteadt D. Endothelial Dysfunction Is Associated with Mortality and Severity of Coagulopathy in Patients with Sepsis and Disseminated Intravascular Coagulation. *Clin Appl Thromb Hemost* 2019; **25**: 1076029619852163 [PMID: 31140293 DOI: 10.1177/1076029619852163]
102 **Dolmatova EV**, Wang K, Mandavilli R, Griendling KK. The effects of sepsis on endothelium and clinical implications. *Cardiovasc Res* 2021; **117**: 60-73 [PMID: 32215570 DOI: 10.1093/cvr/cvaa070]
103 **Inata Y**. Should we treat sepsis-induced DIC with anticoagulants? *J Intensive Care* 2020; **8**: 18 [PMID: 32082582 DOI: 10.1186/s40560-020-0435-8]
104 **108 Mazeraud A**, Righy C, Bouchereau E, et al Septic-associated encephalopathy: a comprehensive review. Neurotherapeutics 2020;17:392-403 [DOI: 10.1007/s13311-020-00862-1]
105 **Chung HY**, Wickel J, Brunkhorst FM, Geis C. Sepsis-Associated Encephalopathy: From Delirium to Dementia? *J Clin Med* 2020; **9** [PMID: 32150970 DOI: 10.3390/jcm9030703]
106 **Desagher S**, Glowinski J, Premont J. Astrocytes protect neurons from hydrogen peroxide toxicity. *J Neurosci* 1996; **16**: 2553-2562 [PMID: 8786431 DOI: 10.1523/JNEUROSCI.16-08-02553.1996]
107 **Cannon G**, Caravati EM, Filloux FM. Hydrogen peroxide neurotoxicity in childhood: case report with unique magnetic resonance imaging features. *J Child Neurol* 2003; **18**: 805-808 [PMID: 14696912 DOI: 10.1177/08830738030180111501]
108 **Ohashi M**, Hirano T, Watanabe K, Katsumi K, Ohashi N, Baba H, Endo N, Kohno T. Hydrogen peroxide modulates synaptic transmission in ventral horn neurons of the rat spinal cord. *J Physiol* 2016; **594**: 115-134 [PMID: 26510999 DOI: 10.1113/JP271449]
109 **Frantseva MV**, Perez Velazquez JL, Carlen PL. Changes in membrane and synaptic properties of thalamocortical circuitry caused by hydrogen peroxide. *J Neurophysiol* 1998; **80**: 1317-1326 [PMID: 9744941 DOI: 10.1152/jn.1998.80.3.1317]
110 **Teepker M**, Anthes N, Fischer S, Krieg JC, Vedder H. Effects of oxidative challenge and calcium on ATP-levels in neuronal cells. *Neurotoxicology* 2007; **28**: 19-26 [PMID: 16870261 DOI: 10.1016/j.neuro.2006.06.001]
111 **Wang Y**, Floor E. Hydrogen peroxide inhibits the vacuolar H+-ATPase in brain synaptic vesicles at micromolar concentrations. *J Neurochem* 1998; **70**: 646-652 [PMID: 9453558 DOI: 10.1046/j.1471-4159.1998.70020646.x]
112 **Kamsler A**, Segal M. Hydrogen peroxide modulation of synaptic plasticity. *J Neurosci* 2003; **23**: 269-276 [PMID: 12514224 DOI: 10.1523/JNEUROSCI.23-01-00269.2003]

113 **Santhanam S**, Venkatraman A, Ramakrishna BS. Impairment of mitochondrial acetoacetyl CoA thiolase activity in the colonic mucosa of patients with ulcerative colitis. *Gut* 2007; **56**: 1543-1549 [PMID: 17483192 DOI: 10.1136/gut.2006.108449]

114 **118 US Department of Health and Human Services**. Chemical Hazards emergency medical management. [cited 3 February 2021] Available from: https://chemm.nlm.nih.gov/countermeasure_sodium-thiosulfate.htm#indication

115 **Pravda J**. Hydrogen peroxide and disease: towards a unified system of pathogenesis and therapeutics. *Mol Med* 2020; **26**: 41 [PMID: 32380940 DOI: 10.1186/s10020-020-00165-3]

116 **Tsang RY**, Al-Fayea T, Au HJ. Cisplatin overdose: toxicities and management. *Drug Saf* 2009; **32**: 1109-1122 [PMID: 19916578 DOI: 10.2165/11316640-000000000-00000]

117 **Nigwekar SU**, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med* 2018; **378**: 1704-1714 [PMID: 29719190 DOI: 10.1056/NEJMra1505292]

118 **Neuwelt EA**, Gilmer-Knight K, Lacy C, Nicholson HS, Kraemer DF, Doolittle ND, Hornig GW, Muldoon LL. Toxicity profile of delayed high dose sodium thiosulfate in children treated with carboplatin in conjunction with blood-brain-barrier disruption. *Pediatr Blood Cancer* 2006; **47**: 174-182 [PMID: 16086410 DOI: 10.1002/pbc.20529]

119 **Enongene EN**, Sun PN, Mehta CS. Sodium thiosulfate protects against acrylonitrile-induced elevation of glial fibrillary acidic protein levels by replenishing glutathione. *Environ Toxicol Pharmacol* 2000; **8**: 153-161 [PMID: 10867374 DOI: 10.1016/s1382-6689(00)00036-3]

120 **Hayden MR**, Tyagi SC, Kolb L, Sowers JR, Khanna R. Vascular ossification-calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease, and calciphylaxis-calcific uremic arteriolopathy: the emerging role of sodium thiosulfate. *Cardiovasc Diabetol* 2005; **4**: 4 [PMID: 15777477 DOI: 10.1186/1475-2840-4-4]

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REVIEW

What we learned in the past year in managing our COVID-19 patients in intensive care units?

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Abstract

Coronavirus disease 2019 is a pandemic, was first recognized at Wuhan province, China in December 2019. The disease spread quickly across the globe, spreading stealthily from human to human through both symptomatic and asymptomatic individuals. A multisystem disease which appears to primarily spread *via* bio aerosols, it has exhibited a wide clinical spectrum involving multiple organ systems with the respiratory system pathology being the prime cause of morbidity and mortality. Initially unleashing a huge destructive trail at Wuhan China, Lombardy Italy and New York City, it has now spread to all parts of the globe and has actively thrived and mutated into new forms. Health care systems and Governments responded initially with panic, with containment measures giving way to mitigation strategies. The global medical and scientific community has come together and responded to this huge challenge. Professional medical societies quickly laid out "expert" guidelines which were conservative in their approach. Many drugs were re formulated and tested quickly with the help of national and international collaborative groups, helping carve out effective treatment strategies and help build a good scientific foundation for evidence-based medicine. Out of the darkness of chaos, we now have an orderly approach to manage this disease both from a public health preventive and therapeutic standpoint. With preventive measures such as masking and social distancing to the development of highly effective and potent vaccines, the public health success of such measures has been tempered by behavioral responses and resource mobilization. From a therapy standpoint, we now have drugs that were promising but now proven ineffective, and those that are effective when given early during viral pathogenesis or later when immune dysregulation has established, and the goal is to help reign in the destructive cascade. It has been a fascinating journey

States

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for mankind and our work here recapitulates the evolution of various aspects of critical care and other inpatient practices which continue to evolve.

Key Words: COVID-19; Respiratory support; Renal replacement therapy; Extracorporeal membrane oxygenator; Medications; Therapeutics

Core Tip: Severe acute respiratory syndrome coronavirus 2 transmission and the inpatient therapeutic management of coronavirus disease 2019 has been subject of immense research in the past one year. Our knowledge and understanding of the virus and the treatment of the disease continue to evolve. We attempt to summarize the progress made in a concise but comprehensive manner along with our insights into future directions.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first reported and widely believed to have originated at Wuhan in the Hubei province, China in late December 2019[1]. It started as a Zoonotic disease and gained a foothold in human population by person-to-person transmission, having evolved into a destructive pandemic infecting more than 100 million people and has caused more than 2.2 Million deaths till date[1,2].

A member of Beta coronaviruses, which includes SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) which have caused localized epidemics in the Asian continent, the SARS-CoV-2 rapidly spread across the globe and has now survived and evolved with mutants due to its ability to stealthily spread by airborne transmission, ability to survive in varying environmental conditions, causing asymptomatic or mild infection in humans with transmission characterized by the ability to infect early on during the prodromal phase of illness, aided generously by "super spreaders"[1,3,4].

The management of the disease has evolved with early conservative guidelines from experts to evidence-based recommendations which continue to evolve every day touching all aspects of care from the use of respiratory assist devices, medication including repurposed drugs, novel and controversial therapies as well as delivery of our critical care services. Here we attempt to capture some of these changes and present the current state of evidence of some of these therapies and services used in the management of COVID-19[5].

INFECTIVITY AND TRANSMISSION CHARACTERISTICS

Since the beginning of the pandemic SARS-CoV-2 duration of shedding, infectivity, and mechanism of transmission of infection have been very keenly studied as they have practical implications. We now have better knowledge and understanding of these characteristics. The viral RNA has been detected by reverse transcriptase-polymerase chain reaction testing from the upper respiratory tract for a mean of 17 d with a maximal duration of 83 d. Likewise, from the lower respiratory tract, the viral RNA has been detected for a mean duration of 17.2 d with a maximal duration of only 35 d. However more importantly the live virus has not been cultured beyond the 9th day of symptom in any study to date. Hence the maximal infectivity is likely in the first week from symptom onset and tapers off subsequently[6].

Respiratory transmission is now considered the predominant mode of infection. Droplets are large particles typically more than 5 microns which are heavier and drop within 6 feet, whereas aerosols are smaller than 5 microns and post evaporation remain suspended like pollens in the air having the ability to travel longer distances [7]. Our current understanding is that the virus is shed as particles across a wide range of sizes[8,9]. A longer duration, closer proximity, forced exhalation of air from a patient with high viral load is now considered necessary for cross-infection to occur with SARS-CoV-2[8]. Logically a "full high-level barrier protection" with Personal Protective Equipment (PPE), N95 mask & Negative pressure room may therefore be necessary when managing a highly symptomatic patient who is excessively coughing, is on high flow oxygen, noninvasive ventilation (NIV), Mechanical ventilator, is undergoing Bronchoscopy or has a Tracheostomy. In all these situations, a large amount of air is being mobilized across the mucosa covered with the virus, enhancing the possibility of viral aerosolization & infection[8]. In fact if the combination of "full barrier precautions" and adherence to clinical practice guidelines are strict, then the likelihood of infection with SARS-CoV-2 in clinical care areas for staff is substantially reduced or insignificant[10].

The role of respiratory assist devices and maneuvers in the pandemic

COVID-19 is a disease that affects multiple organ systems but primarily and disproportionately affects the Respiratory system. Early in the pandemic stemming from the Chinese experience, COVID-19 patients were intubated early when needing more than 5-6 L/min oxygen to avoid aerosolization of SARS-CoV-2 infection to staff and due to the anticipation, that these patients would deteriorate rapidly with the attendant risk of substantial hypoxia during intubation. However it is now apparent that such aggressive measures are not warranted as it places substantial burden on the need for critical care resources[11]. Although not proven to be causative, the early surge of COVID-19 cases in New York city and Italy in early 2020 was notable for very high mortality noted in intubated patients[12,13].

Adult respiratory distress syndrome (ARDS) is the dominant respiratory clinical syndrome seen in COVID-19 patients[13,14] with histopathology primarily characterized by diffuse alveolar damage very similar to SARS-CoV-1 and MERS-CoV infections[15]. ARDS related lung injury and Respiratory mechanics in COVID-19 appear to be similar to non-COVID-19 ARDS; nevertheless substantial controversy exists regarding management in literature which is intriguing and is addressed in our discussion[11,13,14].

Oxygen supplementation and NIV

It is generally accepted that low flow oxygen with a simple face mask or Cannula is used for supplemental oxygen as the first line of support when SaO_2 is less than 88%. The next line of oxygen supplementation is through high flow nasal cannula (HFNC). It provides oxygen at a very high flow rates (40-80 L/min). This oxygen also is heated and humidified to simulate physiological conditions in the airway promoting patient comfort and tolerance[16]. HFNC is essentially a flow generator helping with mucociliary clearance in the airway and improves the Ventilatory function of the lung by providing low levels of functional "Positive end expiratory Pressure (PEEP)" in the respiratory tract[17]. A type 1 surgical mask can substantially reduce particulate aerosol contamination from nasal devices when placed over them[18]. The dispersion of aerosolized particles is higher than a simple mask for HFNC but much less when compared to NIV in simulated experiments[19,20].

NIV such as continuous positive airway pressure (CPAP) and Bi-level alveolar positive airway pressure (BIPAP) are the next line which provides pressure targeted ventilation. CPAP has traditionally been used in acute cardiogenic pulmonary edema by increasing functional residual capacity and therefore oxygenation and compliance. BIPAP in addition to the latter has also been used in acute exacerbation of the chronic obstructive pulmonary disease for counterbalancing inner PEEP with external PEEP and decreasing work of breathing by acting as an inhalation assist device[17]. Both modes of NIV have been traditionally used in obstructive sleep apnea and obesity hypoventilation syndrome[21]. CPAP and BIPAP must be used with a full-face mask to decrease the risk of aerosolization. BIPAP can also be used with a helmet mask (mostly available in Europe). They have been shown to have an acceptable level of aerosolization which can be further attenuated with the help of a well-fitting helmet mask[22].

In general, HFNC is preferred over NIV. HFNC is much more comfortable for the patient as it allows for speech, eating/drinking as well as comfort[17]. But NIV may be preferred in patients who have acute chronic obstructive pulmonary disease (COPD)

exacerbation with hypercarbia, acute pulmonary edema and those who have sleep disordered breathing.

Evidence from non-COVID-19 literature for HFNC and NIV

In the FLORAL trial involving hypercpaneic patients with acute hypoxemic respiratory failure, HFNC was shown to decrease intubation rate which was statistically significant in a sub-group of patients with $Pao_2/Fio_2 < 200$ when compared to non-rebreather mask (≥ 10 L/min) or NIV. Mortality also favored the HFNC group at 90 d when compared to the other two groups in this study[23].

In another study, HFNC was non-inferior to NIV for preventing reintubation and post-extubation respiratory failure in high-risk adults[24].

In another randomised controlled trial involving high-risk adults, the combined use of HFNC and NIV prevented more extubation failures than HFNC alone[25] suggesting that the two modalities can complement each other.

In the LUNG SAFE study, about 15% of ARDS patients were treated with NIV. Failure of NIV was increasingly common with increasing severity of ARDS but mortality was especially higher in patients who had Pao_2/Fio_2 lower than 150 mmHg [26] and hence should be avoided in this subgroup of Moderate to Severe ARDS Patients.

In a systematic review and meta-analysis involving 25 studies and 3804 patients, the use of both helmet and face mask NIV was associated with decreased mortality and endotracheal intubation compared to standard oxygen therapy[27]. However, in sensitivity analysis excluding studies which included COPD exacerbation and congestive heart failure exacerbation, the observed benefit on mortality was not noted. The beneficial effect on mortality was also less certain with patients who had severe ARDS.

Evidence from COVID-19 literature for HFNC and NIV

Good quality data is lacking but some moderate sized retrospective observational studies have been published.

In Lombardy Italy, about 350 of 3988 patients with COVID-19 Pneumonia were treated with NIV, of which 50 percent required intubation. The mortality of the latter group was similar to patients who were intubated on admission to the intensive care units (ICU)[28].

In one published Italian retrospective observational study of 670 patients, the rate of intubation and adjusted mortality did not vary in patients who were treated with High flow oxygen, CPAP and BIPAP[29].

In a study of 110 patients who received non-invasive ventilation *via* helmet for two days, followed by the high flow nasal oxygen therapy or high flow oxygen alone, there was no difference in the ventilator free days at 28 d between NIV and high flow, but patient in the helmet NIV group had decrease in intubation and mechanical ventilation free days, with the *P* value of 0.03[30].

In a systematic review and meta-analysis of non-randomized cohort studies involving about 1897 critically ill patients, there was no statistically detectable difference on all-cause mortality between patients undergoing intubation without *vs* with a prior trial of HFNC/NIV [eight studies, 1128 deaths; 48.9% *vs* 42.5%; risk ratio (RR) 1.11, 95% confidence interval (CI): 0.99-1.25, $P = 0.08$][31].

Monitoring of patients on HFNC and NIV

Patients need to be carefully monitored when on supplemental oxygen devices like high flow or NIV. Intubation should not be withheld when appropriate criteria are met. It is estimated that about 20%-25% of patients can avoid intubation and help preserve Critical resources during the pandemic[17]. Further evidence is needed.

Early vs late intubation

The concept of early *vs* late intubation in COVID-19 pneumonia is controversial which has elicited a fascinating Pros-Con debate[32,33].

Early on, some professional organizations like the Royal College of Anesthetists & Intensive Care Society recommended early intubation to prevent the risk of high environmental contamination with other oxygenation and ventilatory adjuncts like NIV/HFNC[32].Others like the Society of Critical Care Medicine recommended careful monitoring with NIV/HFNC and intubation when the latter failed[34].

A failed NIV followed by intubation can be associated with an increased risk of complications during intubation like hypotension, desaturation, and aspiration with associated increased risk of mortality[35]. While some studies in non-COVID-19

hypoxemic respiratory failure show increased mortality with delayed intubation[35,36] others in COVID-19 hypoxemic respiratory failure showed no such increased mortality[13].

Proponents of early mechanical ventilation emphasize the possibility of "Patient self-inflicted Lung injury (P-SILI) "in the non-intubated critically ill patient with acute hypoxemic respiratory failure which is a collective term for the high minute ventilation, a high respiratory drive of the ARDS patient worsening the preexisting lung injury with increased vascular permeability along with local and global lung over distension[37]. P-SILI in a spontaneously breathing patient is akin to ventilator-induced lung injury in a mechanically ventilated patient[33] and is caused by high pleural pressures and trans pulmonary pressure swings. Lung protective ventilatory strategies using mechanical ventilation along with deep sedation and/or neuromuscular paralysis can prevent P-SILI[37,38]. The endotracheal tube helps gain good control over an unstable airway and regulate oxygen, pressure, and volume[39].

Opponents of early and liberal Mechanical ventilation offer many valid reasons. The concept of P-SILI is relatively new and the evidence supporting it is not very robust [33]. Mechanical ventilation brings along with it a host of complications like delirium secondary to sedation, hemodynamic instability secondary to decreased sympathetic drive and positive pressure ventilation, increased risk of infection, immobilization with increased risk of thromboembolism, neuromuscular paralysis, post-intensive care syndrome with its attendant physical and neurocognitive dysfunction[32]. Intubation and mechanical ventilation are associated with one of the highest risks of aerosolization[40] and for the patient, there is risk of procedure related hypotension, hypoxemia, cardiac arrest, and other complications[41]. During a pandemic conserving critical resources and their judicious use is important and intubating every patient with hypoxemic respiratory failure is going to be unethical[42,43].

No randomized control studies have been published on this topic. The definition of early *vs* late intubation is variable across studies. A few small single-center retrospective studies have reported variable outcomes for delayed *vs* early endotracheal intubation[44-47] with one study reporting worser mortality outcomes for delayed intubation and other three being equivocal.

In a systematic review and meta-analysis of non-randomized cohort studies involving about 9000 critically ill patients compared early (less than 24 h after ICU admission) *vs* late (more than 24 h after ICU admission) intubation found no difference in all-cause mortality(3981 deaths; 45.4% *vs* 39.1%; RR 1.07, 95%CI: 0.99-1.15, $P = 0.08$), duration of mechanical ventilation (1892 patients; MD - 0.58 d, 95%CI: 3.06-1.89 d, $P = 0.65$), ICU length of stay and renal replacement therapy (RRT)[31].

Due to limited data, the question apart from some lively, elegant and animated discussions between experts is probably unsettled[33,48].

Nebulization

SARS-CoV-2 virus transmission occurs predominantly through close contact, poor ventilated environment in a susceptible host *via* droplets/aerosols and less likely through fomites[6,7,9].Transmission *via* bio aerosols from medical procedures like Nebulization and Tracheostomy has been a very valid concern as discussed earlier[49].

As *per* the Global initiative for asthma & The Australian National Asthma Council, the recommendation is to use nebulization therapy only if unavoidable[50,51]. On the contrary, the British National Institute of Health Care and Excellence recommends that patients with COVID-19 can continue using nebulization therapy[52]. Such contrary guidelines and recommendations have sowed doubts in the minds of patients and professional health care practitioners. It is indicative of the fact that the evidence base for these contrary recommendations is not very strong.

Although a continuation of inhalational treatment for chronic respiratory diseases has been universally recommended[51], the optimal mode is less certain. Inhalers have been recommended as they seem to generate fewer aerosols, the drug is contained in the container and less likely to be contaminated by infectious particles, and they also have a low emitted dose[49]. However, either *via* normal exhalation or cough (determined by drug formulation characteristics) induced by the inhaled medication, inhalers can produce exhaled bio aerosols and hence they do not seem to be superior to nebulizer therapy[49].

Theoretically, nebulizer therapy produces an aerosol of the medication in the nebulizer container and hence should not produce infected aerosols unless the container or medication gets contaminated[49]. An aerosol droplet coming in contact with an infected mucous membrane, like in the lung stops being airborne and hence is no longer an aerosol[53]. Hence good hygiene precautions undertaken while using the nebulizer and while loading the medication should prevent the spread of infection by

aerosolization[49,53]. Besides, other precautions to prevent bio aerosolization have been proposed such as the use of viral filters in the circuit of nebulizers/ventilators, use of vibratory mesh nebulizers which separate medication from patient interface including circuits, and good provider/patient hygiene and using mouthpiece with handheld devices[53]. Universally full barrier precautions as discussed earlier should be practiced to limit infection.

Bronchoscopy

At the beginning of the pandemic, many Pulmonary/Bronchology societies made recommendations for COVID-19, but were limited by generalizations, lack of exhaustiveness, and clear guidance was not available due to the novelty of the disease; extrapolation from previous coronavirus pandemics was required[54]. Almost all societies recommended deferring bronchoscopy in non-urgent cases, observing full barrier precautions when performing bronchoscopies, restricting the number of personnel who could be participating in the procedure, limit aerosol producing procedures like nebulization, use of atomizers and jet ventilation[55]. Peri procedurally recommendations included using sedation (or even paralytics when feasible) to avoid coughing, avoiding high flow and high shearing maneuvers, all intended to limit aerosolization. Flexible bronchoscopy is encouraged and rigid bronchoscopy is discouraged with post-procedure recommendations lacking consensus[54]. To avoid cross-contamination or accidental transmission, single-use flexible bronchoscopes are encouraged[54].The patient can wear a mask and a slot can be made for introducing the bronchoscope[54,55].

Certain acceptable indications for bronchoscopy in COVID-19 times include but not exhaustively, symptomatic airway stenosis, symptomatic hemoptysis, migrated stent, therapeutic aspiration of obstructive symptomatic secretions or masses, diagnosis of secondary infections in intubated COVID-19 patients, diagnosis of cancer, and diagnosis of infection in immunocompromised patients[55].

In a single-center, where 241 bronchoscopies were performed on 107 COVID-19 patients, 54 patients (50.5%) had Broncho Alveolar Lavage (BAL) with 35 patients (65%) demonstrating a positive culture. About 1/3rd of intubated patients required bronchoscopy presumably due to thickened white gelatinous secretions (likely due to heated air with less humidification as was recommended by guidelines) or bloody secretions due to high use of anticoagulants. BAL cultures were more likely to be positive (65%) compared to tracheal cultures (45%). 6% of BAL cultures also grew a second organism. The study showed a high rate of secondary infection in COVID-19 patients above and beyond that was diagnosed with tracheal cultures, indicating that under treatment may be driving higher mortality[56].

In another single-center series of 93 intubated patients, 101 bronchoscopies were performed which did not show increased secondary infection when compared to non-covid ventilator associated pneumonia[57].

In general, bronchoscopy has not shown any definitive increase in transmission when proper precautions have been observed[56,57].

Tracheostomy

Tracheostomy has been widely used across the globe for COVID-19 management. Initially, expert guidelines were made available which were very conservative in their recommendations but now we have better evidence to guide our decisions[58]. Certain pertinent issues concerned with Tracheostomy are addressed here.

The Indications for tracheostomy have traditionally not been well defined, dependent on multiple factors and individual circumstances[59]. In the current COVID-19 times, tracheostomies have been performed early (less than 7 to 10 d after intubation) and for very liberal indications with critical care resource utilization as a goal commensurate with principles of "Disaster management"[60-62]. However, guidelines based on several critical considerations including virology of transmission and infectiousness of the patient recommended the timing to be past 10 d and when patients show clinical improvement[59]. This is because it is difficult to predict the clinical trajectory of ARDS patients with COVID-19. After the patient has navigated the first few days of Critical illness and shown clinical improvement, but anticipate prolonged mechanical ventilation, with reasonable pulmonary reserves, the FiO_2 less than 40% and PEEP less than 8, then tracheostomy can be considered[59,60,63,64]. Given that there are advantages and disadvantages to both early and late tracheostomy, and with relatively proven non-inferiority, the timing of tracheostomy like in non-COVID-19 patients has to be individualized[61,63]. In practice, a systematic review and meta-analysis encompassing 462 COVID-19 patients revealed that 250 patients (71.5%) received tracheostomy 14 d after intubation, which is consistent with

conventional practice[65].

Tracheostomy can be performed by the "open or surgical" method in the operating room or by "Percutaneous dilatation" at the patient bedside. Initially, the recommendation was to use the "Open or Surgical" method to minimize exposure to bio aerosol which is potentially more with the percutaneous method[59,64]. However, with diligent and appropriate use of "Full barrier" precautions including PPE with or without a negative pressure room, the increased risk to healthcare personnel has not materialized and the emphasis is now to optimally use available resources as both methods have been proven to be safe[59,62,64,65]. In a pooled analysis of 3060 tracheostomies, 55.7% were created by the open method and 43.4% were created by the percutaneous method[65].

Post-procedural management guidelines suggest to limit staff exposure to bio aerosols have been published and it has been demonstrated that this can be implemented successfully by training new staff members unfamiliar with tracheostomy care, thereby helping free critical ICU resources when necessary[59,62,64].

Post tracheostomy outcome data in COVID-19 patients are now available. In a pooled analysis, of 2890 mechanically ventilated patients 54.9% were reported to have been successfully weaned, of 2628 patients 34.9% were successfully decannulated, and of 2980 patients 513 patients (13.1%) had died[65].

Overall tracheostomy in COVID-19 patients has evolved from the early time of guidelines recommending "abundant caution" to now practice and outcomes which seem to be more consistent with "regular order".

Convalescent plasma and monoclonal antibody

Convalescent plasma has been used to treat many infectious diseases in the past like Influenza, MERS-CoV, Ebola Virus, Influenza, *etc.*, but efficacy and evidence are not firmly established[66,67]. The goal of such passive immunization is to neutralize the infectious organism with the help of naturally formed and passively transferred antibodies[66]. Novel neutralizing monoclonal antibodies (nabs) and nano antibodies have also come into play during the coronavirus pandemic[68].

SARS-CoV-2 virus enters the cell *via* the angiotensin-converting enzyme 2 (ACE2) receptors on the respiratory and gastrointestinal tract epithelium. The SARS–CoV-2 virus has an outer "S" glycoprotein, with S1 and S2 subunits. The S1 subunit has a receptor binding domain along with receptor binding motif, the latter attaches to the ACE2 receptor in the host, and there is a conformational change in the S protein leading to S2 fusing with the host cell wall membrane followed by internalization of the virus into the host cell. The SARS-CoV-2 antibody in the convalescent plasma/nabs can halt the virus from multiplying and establishing a foothold in the host by interfering with receptor attachment, inhibiting wall fusion after attachment, and preventing uncoating of the virus once inside the cytoplasm[68,69].

With COVID-19, convalescent plasma has been widely used from the early days of the pandemic on a compassionate basis with regulatory approval[70]. However; results from various studies have been inconsistent.

Analysis of large observational data and different Randomized control studies show that when plasma with low SARS-CoV-2 antibody titer or when used later in the disease trajectory or both results in lack of survival benefit, does not halt the progression of the disease or help with stabilization of symptoms[70-72]. COVID-19 patients with moderate to severe ARDS, especially intubated patients do not derive any benefit from convalescent plasma[70-73].

On the contrary, when the plasma has high antibody titer, and patients receive early on at symptom onset in the community or even during early hospitalization when patients have mild to moderate disease, it results in better survival, disease stabilization and halts the progression of the disease[70,73,74].

As *per* Food and Drug Administration (FDA), high titter convalescent plasma corresponds to a neutralizing antibody titer of ≥ 250 in the Broad Institute's neutralizing antibody assay, a signal-to-cutoff of ≥ 12 in the Ortho VITROS immunoglobulin G (IgG) assay, or a level of ≥ 1:2880 in the Mount Sinai COVID-19 ELISA IgG Antibody Test[75].

The role of passive immunization with convalescent plasma or Neutralizing antibodies is to inhibit viral replication early in the disease when the host does not have sufficient antibodies of its own. Once the infection is established, native antibodies are formed and inflammatory processes are at work, at which point the passively transfused antibodies are not helpful[76].

Similarly neutralizing Monoclonal antibodies like Bamlanivimab were found to help reduce viral load, and hospitalization in recently diagnosed mild to moderate COVID-19 disease as outpatient especially in patients with co-morbidities across age groups,

especially in elderly, but not useful in hospitalized severely ill COVID-19 patients[77]. In the yet to be published Blaze-2 trial, Bamlanivimab used as a prophylaxis in nursing home and assisted care home residents were found to decrease symptoms and even have a survival advantage when compared to placebo[78]. And although peer review is pending, this appears to be a promising therapy when used in high-risk patients either as prophylaxis or early disease complementing the huge anticipated benefit of vaccine administration on a large scale.

The FDA has updated its Emergency use authorization on February 4, 2021 and now limits the use of high titer COVID-19 convalescent plasma only for the treatment of hospitalized patients with COVID-19 early in the disease course and to those hospitalized patients who have impaired humoral immunity and cannot produce an adequate antibody response[79].

The recovery trial has reported its findings in a preprint article on the use of high titer convalescent plasma in hospitalized patients which is yet to be peer reviewed [80]. 5795 patients were randomly allocated to receive convalescent plasma and 5763 to usual care alone. There was no significant difference in 28-d mortality between the two groups: 1398 (24%) of 5795 patients allocated convalescent plasma and 1408 (24%) of 5763 patients allocated usual care died within 28 d (RR 1.00; 95%CI: 0.93-1.07; $P = 0.93$). Similarly there was no change in the proportion of patients discharged from hospital, progression of patients not on mechanical ventilation towards intubation, successful cessation from mechanical ventilation or need for RRT. However, the mean number of days from symptom onset was 9, and therefore likely the plasma was not used early enough in the disease course.

Glucocorticoids

Glucocorticoids are one of the oldest, well known, inexpensive, immunomodulatory agents with wide ranging immunosuppressive, anti-inflammatory and anti-allergic effect. They also have a multitude of adverse effects as well[81]. It was therefore natural to test their effectiveness as a therapeutic agent for COVID-19, and although some of the earlier studies did not show any benefit, the "RECOVERY Trial" was the earliest well conducted randomized sontrol trial that showed survival benefit in severely ill patients needing supplemental oxygen and ventilation[82]. The latter study showed that there was mortality benefit with use of dexamethasone.

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care[77].

Overall 17 percent relative reduction in mortality (22.9 *vs* 25.7 percent, RR 0.83, 95%CI: 0.75-0.93),

Patients on invasive mechanical ventilation or (ECMO) at baseline–36 percent relative reduction (29.3 *vs* 41.4 percent, RR 0.64, 95%CI: 0.51-0.81). Age-adjusted analysis suggested a 12.3 percent absolute mortality reduction.

Patients on noninvasive oxygen therapy (including NIV) at baseline–18 percent relative reduction (23.3 *vs* 26.2 percent, RR 0.82, 95%CI: 0.72-0.94). Age-adjusted analysis suggested a 4.1 percent absolute mortality reduction.

Currently as *per* a pooled meta-analysis, the use of glucocorticoids is estimated to cause 31 fewer deaths *per* 1000 [odds ratio (OR) 0.87, 95%CI: 0.77 to 0.98; risk difference 31 fewer *per* 1000, 95%CI: 55 fewer to 5 fewer], risk of mechanical ventilation is reduced by 28 *per* 1000 (OR 0.73, 0.58 to 0.92; risk difference 28 fewer *per* 1000, 45 fewer to 9 fewer), and duration of hospital stay is reduced by almost 1 d (mean difference -0.99 d, -1.36 to -0.64), all results estimated to be of moderate certainty[83].

With this the use of glucocorticoids became well established as standard of care for the treatment of severely ill COVID-19 patients needing supplemental oxygen and or ventilation. This has been followed by the question whether the standard 6 milligram Dexamethasone *per* day therapy which was used in the RECOVERY TRIAL is sufficient a dose or if there is an incremental benefit by dose increase? Also, another pertinent question is whether there is any benefit of targeting any other specific immune pathways.

While Randomized control data involving the inhibition of complement C5 inhibitor, raviluzumab has not been shown to be of benefit as *per* preliminary unpublished data[84], the role of Interleukin-6 inhibitor, tocilizumab has been quite intriguing.

Tocilizumab

Tocilizumab is an interleukin 6 receptor antagonist monoclonal antibody that has been used to treat patients with COVID-19 respiratory and organ failure targeting a key step in inflammatory mediated damage[68]. Early treatment data in observational and randomized control studies, not involving many critically ill patients and without

Glucocorticoid use showed that Tocilizumab was safe but did not have any significant Clinical outcomes[85-87]. There were six small trials which did not show any significant benefit from Tocilizumab[88]. However, data from "STOP COVID"-a large observational study and "REMAP CAP"-A well designed open label international randomized control study consisting of 803 patients, suggest that "the early use of Tocilizumab on entry to ICU" may have important survival and other outcome benefits in the short term which was not seen in less sick patients studied in randomized control trials outside the ICU[85-87,89]. This was especially noted in patients who had ICU admission within 3 d of symptom onset[89] or had evidence of organ failure on admission to ICU[87]. Participants in the Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) study also had a relatively larger proportion of patients on glucocorticoids (more than 80%) compared to other studies[86,87]. In "REMAP-CAP" Tocilizumab (n = 353) and Sarilumab (n = 48) each reduced in-hospital mortality compared with standard of care (28 and 22 *vs* 36 percent; OR for hospital survival 1.64, 95%CI: 1.14-2.35 for Tocilizumab and 2.01, 95%CI: 1.18-4.1 for Sarilumab).

The Tocilizumab arm of RECOVERY TRIAL reported preliminary results which are undergoing peer review[88]. This was an open label randomized placebo-controlled trial in which 82% patients took glucocorticoids like dexamethasone. 2022 patients received tocilizumab and 2094 received standard of care. To be eligible for randomization, patients with COVID-19 were to have hypoxia (SpO_2 < 92%) and C-reactive protein more than 75 mg/dL.

Of 596 (29%) patients in the Tocilizumab group and 694 (33%) patients in the usual care group died (RR 0.86; 95%CI: 0.77-0.96; P = 0.007) at 28 d, an absolute difference of 4%. This translates into Numbers Needed to Treat for saving one life of 25.

Tocilizumab also increased the probability of being discharged alive within 28 d from 47% to 54% (RR 1.23, 95%CI: 1.12-1.34, P < 0.0001).

Among patients not on invasive mechanical ventilation when entered into the trial, Tocilizumab significantly reduced the chance of progressing to invasive mechanical ventilation or death from 38% to 33% (RR 0.85, 95%CI: 0.78-0.93, P = 0.0005).

Allocation to Tocilizumab reduced the use of all forms of dialysis (5% *vs* 7%, RR 0.75, 95%CI: 0.59-0.96, P = 0.02).

Tocilizumab did not have any effect on the chance of successful cessation of invasive mechanical ventilation.

These benefits were seen in all patient subgroups, including those requiring oxygen *via* a simple face mask through to those requiring mechanical ventilators in an intensive care unit.

Tocilizumab is estimated to reduce the relative risk of death by 14% and reduced the time spent in hospital by 5 d when used for patients on oxygen and in addition to the corticosteroid dexamethasone[90].

Taken together data from all 8 trials, use of tocilizumab was associated with 13% proportional reduction in 28-d mortality (death RR 0.87, 95%CI: 0.79-0.96, P = 0.005). It is noteworthy that these mortality benefits were noted in the RECOVERY TRIAL only in patients receiving concomitant steroids.

In summary, it appears that in severely ill COVID-19 patients with hypoxia accompanied by hyper inflammatory state, the early concomitant use of glucocorticoids and Tocilizumab improves outcomes including survival, organ support and progression of disease, suggesting additive or synergistic effect with these two agents.

This beneficial data appears to be quite specific for Tocilizumab, as the numbers of patients with Sarilumab in REMAP-CAP study were few. Trials involving Sarilumab are in progress and results are expected in the future[88].

The United Kingdom government and Center for disease control have expeditiously approved the use of Tocilizumab based on data from REMAP-CAP and RECOVERY TRIALS[90,91]. Other government and Professional societies are expected to update their guidelines soon as well.

Remdesivir

Remdesivir is an inhibitor of "viral RNA dependent RNA polymerase" which inhibits SARS-COV-2 *in vitro*[92] but has not been shown to decrease viral load when compared to placebo[93]. It has been studied extensively in clinical trials and the findings are summarized below.

The outcome data has been measured using the multipoint ordinal scale with each number denoting a particular "clinical status" and the changes are measured and reported accordingly[92-94].

In the international, multicentric auditory consonant trigram test-1 study conducted by the National Institute of Allergy and Infectious Diseases and others, 541 patients were assigned to Remdesivir and 521 to placebo in a double-blind placebo-controlled trial; the study drug was given intravenously for 10 d. A significant number of patients had severe disease with SpO_2 less than 94% by definition and requiring supplemental oxygen. It reported a primary outcome of improved median recovery time of 10 d compared to 15 d with placebo. There was a trend to improvement in mortality which was not statistically significant, 11.4% and 15.2% in two groups, respectively [hazard ratio (HR) 0.73; 95%CI: 0.52-1.03] by day 29. In sub-group analysis, there was mortality benefit noted in patients who were on simple low flow oxygen, (HR 0.30; 95%CI: 0.14-0.64). Remdesivir also showed shorter hospital length of stay, reduced disease progression, and lesser utilization of respiratory assist devices like oxygen, invasive mechanical ventilation, and ECMO[92].

In the World health organization led SOLIDARITY trial[95], which was conducted at multiple sites in 30 countries, 11330 adults underwent randomization. Death occurred in 301 of 2743 patients receiving Remdesivir and in 303 of 2708 receiving its control (RR 0.95; 95%CI: 0.81-1.11; $P = 0.50$) showing no survival benefit. In this study which had good adherence, Remdesivir was given intravenously for 10 d. Remdesivir did not reduce the incidence of new ventilation.

In another randomized control trial, for patients with moderate clinical disease (Pulmonary infiltrates with SpO_2 more than 94% by definition); Remdesivir did not demonstrate any difference in clinical status when compared to placebo after a 10-d course. Interestingly, the same study showed improvement in clinical status after a 5-d course. The study was confounded by open-label design and imbalances with co-therapy and therefore the significance is unknown[96].

Other randomized control trials did not show any difference in clinical status outcome between a 5 and a 10-d course of Remdesivir[33,34] and the drug is generally safe with no significant adverse effects[92,94,96,97].

Barcitinib, an oral selective Janus kinase inhibitor 1 and 2 inhibitors impair cell entry of the SARS-CoV-2 virus and inhibits cellular signaling pathway. It has been tested in RCT in combination with Remdesivir and compared to placebo it has improved median time to recovery by 1 d (RR for recovery, 1.16; 95%CI: 1.01-1.32; $P = 0.03$). At 15 d, time to recovery favors the drug combination. In sicker patients who are on NIV or high flow oxygen the time to recovery was 10 d compared to 18 d. (RR for recovery, 1.51; 95%CI: 1.10-2.08). However, given the lack of efficacy for survival, in practice, it can be used with Remdesivir, when steroids are contraindicated[98].

In summary in patients with severe disease (SpO_2 less than 94% with pulmonary infiltrates) and risk of the hyper inflammatory response, Remdesivir may help improve time to clinical recovery and reduce duration of hospitalization, but does not improve survival[92-94,99-101]. It is likely not very helpful or may have very modest benefits in patients who have mild to moderate disease (Pulmonary infiltrates with SpO_2 more than 94%)[34,96,100]. As *per* a meta-analysis, it may help to reduce the need for ventilation but the effect may not be large. It may help to reduce serious adverse events and may aid with some recovery. For non-ventilated patients, a 5 d course compared to 10 d course results in reduced costs, more benefits and less harm[101].

With lack of improvement in survival, the soft benefit of improvement in clinical status, the need to be given by intravenous infusion often as an inpatient over 5 d, lack of cost effectiveness and an endless number of patients with this pandemic, remdesivir is not an optimal answer where the treatment needs to be inexpensive, scalable and equitable[99,101,102]. However since it does reduce time to clinical recovery and reduces duration of hospitalization among survivors, it can help free up inpatient resources in a pandemic and hence gets approval from FDA and Infectious disease society of America[101,103].

Hydroxychloroquine

It is an immunomodulatory drug that has been used extensively in rheumatological disorders. It was repurposed for use in COVID-19 patients and many governments around the world including the United States allowed emergency authorization for its use. Its mechanism of action appears to be by inhibiting glycosylation of ACE2 receptors and increasing the pH of endosomes, in effect preventing virus entry into the cells[104,105].

Many studies have been performed with or without concomitant use of azithromycin compared to placebo after initial case reports and non-randomized studies showed efficacy for the drug against SARS-CoV-2[104]. However, none of the randomized control trials, systematic reviews, and meta-analyses, with or without Azithromycin has shown any benefit for Hydroxychloroquine with regards to survival

[92,104,105]. Likewise, there is no benefit with regards to the length of hospitalization, virological cure rate, clinical status score based on a multipoint ordinal scale, need for mechanical ventilation, and radiological improvement[92,104,105]. There was concern over QT prolongation due to both hydroxychloroquine and azithromycin having those properties as well as concern for the possibility of other side effects without much proven benefit as noted before[104,106]. Currently, both these drugs are not used for COVID-19.

ECMO and COVID-19

ECMO is a resource-intensive therapy that has been used when conventional critical care management has failed to help the patient[107]. It has been used in previous pandemics like pandemic influenza A with variable success[108].

It is recommended by experts that ECMO be offered only at experienced centers that have adequate manpower and material resources as well as expertise in managing them, as every aspect of its care from patient selection, maintenance and liberation is highly specialized and nuanced[107]. In fact when regions are under crises level of care amid a surge of cases, then it may be difficult to offer highly resource-intensive therapies like ECMO[107].

The indications, contraindications, and general principles of ECMO care in COVID-19 remain the same[107] with some finer changes to approach and management. It is preferred that aerosolization of the virus is limited and hence transportation is restricted. Cannulation is best performed at the bedside in the ICU. Tracheostomy which is often performed to help lighten sedation and facilitate decannulation needs to be restricted. All personnel need to observe full barrier precautions[107]. Nevertheless, there is evidence that tracheostomy can be safely managed with standard full barrier precautions as mentioned elsewhere in this article and likely guidelines may change. The patient may not be able to be prone due to cannula and likewise, mobilization may be restricted[107].

Patients with COVID-19 often require deep sedation due to various factors and hence post ECMO delirium may need more supportive ICU care or discharge to specialized rehabilitation centers[107,109]. Veno venous ECMO is the most commonly used ECMO for respiratory failure and outcomes are better with this modality compared to veno arterial ECMO which is used only when concomitant circulatory support is necessary[107,109]. Given the high incidence of thrombosis in COVID-19, therapeutic anticoagulation keeping activated partial thromboplastin time 1.5 to 2.5 times normal is recommended often bordering on the higher side[107] to prevent clot formation in the oxygenator and other parts of the circuit.

Initially reports suggested poor outcomes with ECMO[110] with mortality in the range of 80%-100% but subsequently, a report from the Extracorporeal Life Support Organization registry which included only experienced centers suggested that the 90-d mortality in more than 1000 carefully selected patients was about 40% and this compares reasonably well with non-COVID-19 patients, indicating that when patient selection is optimal and with the application of best principles of standardized care, the outcomes can be optimal in COVID-19[109].

RRT

RRT is a term that denotes a process of replacing the non-endocrine function of the kidney in acute or chronic kidney injury/disease encompassing filtration across the permeable membrane, exchange of solute and electrolytes along with the removal of fluid[111]. There are different modalities which include standard intermittent hemodialysis (IHD), continuous RRT (CRRT), prolonged intermittent RRT (PIRRT), and peritoneal dialysis[112]. CRRT or its variates are preferred in critically ill patients due to their superior ability for fluid removal, causing less hemodynamic instability and consistent metabolic control[112]. It also provides for predictable dosing of medication in renal failure. However, CRRT is not superior to IHD when it comes to survival or Renal recovery[112].

CRRT functions by way of three different mechanisms namely convection, diffusion, and adsorption by the filtering membrane[113]. Different modalities or techniques which employ one of these machines are used such as simple diffusion (continuous venovenous hemodialysis), convection (continuous venovenous hemofiltration), or a combination of both (continuous venovenous hemodiafiltration)[114]. No one technique is superior to the other overall and employing any of them is a matter of availability, patient characteristics, and clinician judgment or preference[114]. Timing of RRT, whether early or late after diagnosis of acute kidney injury (AKI) and establishing indication for RRT has been an important question for many well-conducted clinical trials, largely demonstrating equivocal outcomes[113].

There is a paucity of COVID-19 data for RRT. Recommendations from guidelines have essentially been an extension from the non-COVID-19 population with emphasis on limiting staff exposure and optimal utilization of resources during the pandemic [114]. Full standard barrier precautions for staff taking care of ICU patients are recommended[114]. CRRT is ideal for ICU patients which can be managed by ICU nurses but if limited PIRRT can be used which will optimize resource utilization[114]. IHD consumes more specialized resources and equipment along with a dedicated dialysis nurse in full attendance for the duration of the session and is, therefore, less preferred[112]. Access to CRRT is essential with the right internal jugular vein being preferred especially if proning followed by femoral access, left internal jugular vein, and subclavian veins[112].

COVID-19 has been recognized as a prothrombotic disease having consequences for filter life, and as such regional citrate anticoagulation can be used if already in use in the institution. The latter should not be started if such practices are not already in vogue[113,115]. Systemic anticoagulation with low molecular weight heparin or Ultra fractionated heparin or other agents may be necessary to prolong the life of the circuit but specific evidence-based anticoagulation protocols are lacking in the literature [116]. Extracorporeal blood purification with RRT has been proposed as a therapeutic strategy to remove cytokines and other biological immune mediators to improve clinical outcomes. However, evidence for such therapies is currently lacking and is recommended only in the context of clinical trials[116,117].

In a systematic review of COVID-19 patients with AKI, involving 51 studies and 21531 patients, the incidence of AKI was found to be 12.3%. Patients with transplants had a higher rate of AKI at 38.9% (290 patients) and 39% in ICU patients (565 patients). Patients who did not survive had higher rates of AKI at 42% (1745 patients)[118].

RRT use was reported in 39 studies involving 17,664 patients. With overall use of 5.4% with higher rates noted in 16.3% in ICU patients (776 patients), and 15.6% in transplant patients (117 patients)[118]. AKI was more common in studies from North America, followed by Europe, and was least noted in China[118]. There is increasing evidence that both AKI and the need for RRT are important factors influencing survival in COVID-19 patients[112].

CONCLUSION

It was Sir William Osler who inspired by Thomas Carlisle said, "It is not our goal to see what lies dimly in the distance but to do what lies at hand".

The COVID-19 pandemic has continued to teach us many important medical, social, political, economic, and humane lessons at a huge cost. Early on with a limited understanding of the virus, its transmission, spread in the community and the medical management of the disease, our response as a global community was reactive, guided by abundant caution. Medical practices and literature consisted of non-peer-reviewed articles, case reports, and case series consisting of incomplete and non-standardized data resulting in approaches and clinical management which were not scientifically sound, exposing patients to potentially nonbeneficial or even harmful treatment strategies[119,120].

Organized efforts to develop sound epidemiological, demographic, and evidence-based data resulted in governmental organizations (*e.g.*, United Kingdom based Recovery trial), international trial networks (*e.g.*, REMAP-CAP), The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study COVID-19 Registry and others who were well-positioned to rapidly deploy pragmatic trials, design data collection networks to meet data analytic needs in response to the COVID-19 pandemic[119,120].

As evident from our review, the application of sound scientific evidence-based management principles distilled from decades of research in the past, with some accommodations in practices specific to the SARS-CoV-2, mitigation strategies, along with the careful implementation of disaster management principles in times of surge have resulted in better and superior outcomes. This is borne out by the fact that although outcomes have varied highly between centers[121], they have generally improved with time[122], especially when health care delivery systems are not stressed due to surge[123]. This is evident by one organization's meticulous and highly diligent efforts to manage the pandemic by way of standardized, protocolized management principles accommodating new information as well as providing room for research opportunities[124]. This along with rapid large-scale effective immunization provides us hope to get back our lives and business back to normal

soon.

REFERENCES

1 **Shah A**, Kashyap R, Tosh P, Sampathkumar P, O'Horo JC. Guide to Understanding the 2019 Novel Coronavirus. *Mayo Clin Proc* 2020; **95**: 646-652 [PMID: 32122636 DOI: 10.1016/j.mayocp.2020.02.003]

2 **Medicine JHU**. Coronavirus resource center. 2021. [cited 16 January 2021]. Available from: https://origin-coronavirus.jhu.edu/

3 **Lauring AS**. Within-Host Viral Diversity: A Window into Viral Evolution. *Annu Rev Virol* 2020; **7**: 63-81 [PMID: 32511081 DOI: 10.1146/annurev-virology-010320-061642]

4 **Morris DH**, Yinda KC, Gamble A, Rossine FW, Huang Q, Bushmaker T, Fischer RJ, Matson MJ, van Doremalen N, Vikesland PJ, Marr LC, Munster VJ, Lloyd-Smith JO. The effect of temperature and humidity on the stability of SARS-CoV-2 and other enveloped viruses. *bioRxiv* 2020 [PMID: 33083797 DOI: 10.1101/2020.10.16.341883]

5 **Singh R**, Shaik L, Mehra I, Kashyap R, Surani S. Novel and Controversial Therapies in COVID-19. *Open Respir Med J* 2020; **14**: 79-86 [PMID: 33717367 DOI: 10.2174/1874306402014010079]

6 **Cevik M**, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe* 2021; **2**: e13-e22 [PMID: 33521734 DOI: 10.1016/S2666-5247(20)30172-5]

7 **Klompas M**, Baker MA, Rhee C. Airborne Transmission of SARS-CoV-2: Theoretical Considerations and Available Evidence. *JAMA* 2020; **324**: 441-442 [PMID: 32749495 DOI: 10.1001/jama.2020.12458]

8 **Klompas M**, Baker M, Rhee C. What Is an Aerosol-Generating Procedure? *JAMA Surg* 2021; **156**: 113-114 [PMID: 33320188 DOI: 10.1001/jamasurg.2020.6643]

9 **Morawska L**, Johnson GR, Ristovski ZD, Hargreaves M, Mengersen K, Corbett S, Chao CYH, Li Y, Katoshevski D. Size distribution and sites of origin of droplets expelled from the human respiratory tract during expiratory activities. *J Aerosol Sci* 2009; **40**: 256-269 [DOI: 10.1016/j.jaerosci.2008.11.002]

10 **Chandel A**, Patolia S, Brown AW, Collins AC, Sahjwani D, Khangoora V, Cameron PC, Desai M, Kasarabada A, Kilcullen JK, Nathan SD, King CS. High-flow nasal cannula in COVID-19: Outcomes of application and examination of the ROX index to predict success. *Res Care* 2020 [DOI: 10.4187/respcare.08631]

11 **Rola P**, Farkas J, Spiegel R, Kyle-Sidell C, Weingart S, Duggan L, Garrone M, Thomas A. Rethinking the early intubation paradigm of COVID-19: time to change gears? *Clin Exp Emerg Med* 2020; **7**: 78-80 [PMID: 32521584 DOI: 10.15441/ceem.20.043]

12 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]

13 **Grasselli G**, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, Laffey J, Carrafiello G, Carsana L, Rizzuto C, Zanella A, Scaravilli V, Pizzilli G, Grieco DL, Di Meglio L, de Pascale G, Lanza E, Monteduro F, Zompatori M, Filippini C, Locatelli F, Cecconi M, Fumagalli R, Nava S, Vincent JL, Antonelli M, Slutsky AS, Pesenti A, Ranieri VM; collaborators. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *Lancet Respir Med* 2020; **8**: 1201-1208 [PMID: 32861276 DOI: 10.1016/S2213-2600(20)30370-2]

14 **Fan E**, Beitler JR, Brochard L, Calfee CS, Ferguson ND, Slutsky AS, Brodie D. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? *Lancet Respir Med* 2020; **8**: 816-821 [PMID: 32645311 DOI: 10.1016/S2213-2600(20)30304-0]

15 **Deshmukh V**, Motwani R, Kumar A, Kumari C, Raza K. Histopathological observations in COVID-19: a systematic review. *J Clin Pathol* 2021; **74**: 76-83 [PMID: 32817204 DOI: 10.1136/jclinpath-2020-206995]

16 **Spoletini G**, Alotaibi M, Blasi F, Hill NS. Heated Humidified High-Flow Nasal Oxygen in Adults: Mechanisms of Action and Clinical Implications. *Chest* 2015; **148**: 253-261 [PMID: 25742321 DOI: 10.1378/chest.14-2871]

17 **Raoof S**, Nava S, Carpati C, Hill NS. High-Flow, Noninvasive Ventilation and Awake (Nonintubation) Proning in Patients With Coronavirus Disease 2019 With Respiratory Failure. *Chest* 2020; **158**: 1992-2002 [PMID: 32681847 DOI: 10.1016/j.chest.2020.07.013]

18 **Leonard S**, Atwood CW Jr, Walsh BK, DeBellis RJ, Dungan GC, Strasser W, Whittle JS. Preliminary Findings on Control of Dispersion of Aerosols and Droplets During High-Velocity Nasal Insufflation Therapy Using a Simple Surgical Mask: Implications for the High-Flow Nasal Cannula. *Chest* 2020; **158**: 1046-1049 [PMID: 32247712 DOI: 10.1016/j.chest.2020.03.043]

19 **Hui DS**, Chow BK, Lo T, Tsang OTY, Ko FW, Ng SS, Gin T, Chan MTV. Exhaled air dispersion

during high-flow nasal cannula therapy *versus* CPAP *via* different masks. *Eur Respir J* 2019; **53** [PMID: 30705129 DOI: 10.1183/13993003.02339-2018]

20 **Hui DS**, Hall SD, Chan MT, Chow BK, Tsou JY, Joynt GM, Sullivan CE, Sung JJ. Noninvasive positive-pressure ventilation: An experimental model to assess air and particle dispersion. *Chest* 2006; **130**: 730-740 [PMID: 16963670 DOI: 10.1378/chest.130.3.730]

21 **Masa JF**, Pépin JL, Borel JC, Mokhlesi B, Murphy PB, Sánchez-Quiroga Maria Á. Obesity hypoventilation syndrome. *Eur Respir Rev* 2019; **28**: 180097 [PMID: 30872398 DOI: 10.1183/16000617.0097-2018]

22 **Ferioli M**, Cisternino C, Leo V, Pisani L, Palange P, Nava S. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. *Eur Respir Rev* 2020; **29** [PMID: 32248146 DOI: 10.1183/16000617.0068-2020]

23 **Frat JP**, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottereau A, Devaquet J, Nseir S, Razazi K, Mira JP, Argaud L, Chakarian JC, Ricard JD, Wittebole X, Chevalier S, Herbland A, Fartoukh M, Constantin JM, Tonnelier JM, Pierrot M, Mathonnet A, Béduneau G, Delétage-Métreau C, Richard JC, Brochard L, Robert R; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; **372**: 2185-2196 [PMID: 25981908 DOI: 10.1056/NEJMoa1503326]

24 **Hernández G**, Vaquero C, Colinas L, Cuena R, González P, Canabal A, Sanchez S, Rodriguez ML, Villasclaras A, Fernández R. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial. *JAMA* 2016; **316**: 1565-1574 [PMID: 27706464 DOI: 10.1001/jama.2016.14194]

25 **Thille AW**, Muller G, Gacouin A, Coudroy R, Decavèle M, Sonneville R, Beloncle F, Girault C, Dangers L, Lautrette A, Cabasson S, Rouzé A, Vivier E, Le Meur A, Ricard JD, Razazi K, Barberet G, Lebert C, Ehrmann S, Sabatier C, Bourenne J, Pradel G, Bailly P, Terzi N, Dellamonica J, Lacave G, Danin PÉ, Nanadoumgar H, Gibelin A, Zanre L, Deye N, Demoule A, Maamar A, Nay MA, Robert R, Ragot S, Frat JP; HIGH-WEAN Study Group and the REVA Research Network. Effect of Postextubation High-Flow Nasal Oxygen With Noninvasive Ventilation vs High-Flow Nasal Oxygen Alone on Reintubation Among Patients at High Risk of Extubation Failure: A Randomized Clinical Trial. *JAMA* 2019; **322**: 1465-1475 [PMID: 31577036 DOI: 10.1001/jama.2019.14901]

26 **Bellani G**, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, Esteban A, Gattinoni L, Bumbasirevic V, Piquilloud L, van Haren F, Larsson A, McAuley DF, Bauer PR, Arabi YM, Ranieri M, Antonelli M, Rubenfeld GD, Thompson BT, Wrigge H, Slutsky AS, Pesenti A; LUNG SAFE Investigators; ESICM Trials Group. Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome. Insights from the LUNG SAFE Study. *Am J Respir Crit Care Med* 2017; **195**: 67-77 [PMID: 27753501 DOI: 10.1164/rccm.201606-1306OC]

27 **Ferreyro BL**, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, Ryu MJ, Saskin R, Wunsch H, da Costa BR, Scales DC. Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-analysis. *JAMA* 2020; **324**: 57-67 [PMID: 32496521 DOI: 10.1001/jama.2020.9524]

28 **Grasselli G**, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, Cattaneo S, Cereda D, Colombo S, Coluccello A, Crescini G, Forastieri Molinari A, Foti G, Fumagalli R, Iotti GA, Langer T, Latronico N, Lorini FL, Mojoli F, Natalini G, Pessina CM, Ranieri VM, Rech R, Scudeller L, Rosano A, Storti E, Thompson BT, Tirani M, Villani PG, Pesenti A, Cecconi M; COVID-19 Lombardy ICU Network. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med* 2020; **180**: 1345-1355 [PMID: 32667669 DOI: 10.1001/jamainternmed.2020.3539]

29 **Franco C**, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, Scala R, Malerba M, Carlucci A, Negri EA, Spoladore G, Arcaro G, Tillio PA, Lastoria C, Schifino G, Tabbì L, Guidelli L, Guaraldi G, Ranieri VM, Clini E, Nava S. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. *Eur Respir J* 2020; **56** [PMID: 32747398 DOI: 10.1183/13993003.02130-2020]

30 **Grieco DL**, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, Montomoli J, Falò G, Tonetti T, Cutuli SL, Pintaudi G, Tanzarella ES, Piervincenzi E, Bongiovanni F, Dell'Anna AM, Delle Cese L, Berardi C, Carelli S, Bocci MG, Montini L, Bello G, Natalini D, De Pascale G, Velardo M, Volta CA, Ranieri VM, Conti G, Maggiore SM, Antonelli M; Group C-IGS. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. *JAMA* 2021; **325**: 1731-1743 [PMID: 33764378 DOI: 10.1001/jama.2021.4682]

31 **Papoutsi E**, Giannakoulis VG, Xourgia E, Routsi C, Kotanidou A, Siempos II. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. *Crit Care* 2021; **25**: 121 [PMID: 33766109 DOI: 10.1186/s13054-021-03540-6]

32 **Cabrini L**, Ghislanzoni L, Severgnini P, Landoni G, Baiardo Redaelli M, Franchi F, Romagnoli S. Early versus late tracheal intubation in COVID-19 patients: a pro-con debate also considering heart-lung interactions. *Minerva Cardioangiol* 2020 [PMID: 33059400 DOI: 10.23736/S0026-4725.20.05356-6]

33 **Tobin MJ**, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-

19. *Ann Intensive Care* 2020; **10**: 78 [PMID: 32519064 DOI: 10.1186/s13613-020-00692-6]
34 **Alhazzani W**, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, Du B, Aboodi M, Wunsch H, Cecconi M, Koh Y, Chertow DS, Maitland K, Alshamsi F, Belley-Cote E, Greco M, Laundy M, Morgan JS, Kesecioglu J, McGeer A, Mermel L, Mammen MJ, Alexander PE, Arrington A, Centofanti JE, Citerio G, Baw B, Memish ZA, Hammond N, Hayden FG, Evans L, Rhodes A. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med* 2020; **48**: e440-e469 [PMID: 32224769 DOI: 10.1097/CCM.0000000000004363]
35 **Mosier JM**, Sakles JC, Whitmore SP, Hypes CD, Hallett DK, Hawbaker KE, Snyder LS, Bloom JW. Failed noninvasive positive-pressure ventilation is associated with an increased risk of intubation-related complications. *Ann Intensive Care* 2015; **5**: 4 [PMID: 25852964 DOI: 10.1186/s13613-015-0044-1]
36 **Kangelaris KN**, Ware LB, Wang CY, Janz DR, Zhuo H, Matthay MA, Calfee CS. Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome. *Crit Care Med* 2016; **44**: 120-129 [PMID: 26474112 DOI: 10.1097/CCM.0000000000001359]
37 **Brochard L**, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. *Am J Respir Crit Care Med* 2017; **195**: 438-442 [PMID: 27626833 DOI: 10.1164/rccm.201605-1081CP]
38 **Marini JJ**, Gattinoni L. Management of COVID-19 Respiratory Distress. *JAMA* 2020; **323**: 2329-2330 [PMID: 32329799 DOI: 10.1001/jama.2020.6825]
39 **Tobin MJ**, Laghi F, Jubran A. Ventilatory failure, ventilator support, and ventilator weaning. *Compr Physiol* 2012; **2**: 2871-2921 [PMID: 23720268 DOI: 10.1002/cphy.c110030]
40 **Weissman DN**, de Perio MA, Radonovich LJ Jr. COVID-19 and Risks Posed to Personnel During Endotracheal Intubation. *JAMA* 2020; **323**: 2027-2028 [PMID: 32338710 DOI: 10.1001/jama.2020.6627]
41 **Yao W**, Wang T, Jiang B, Gao F, Wang L, Zheng H, Xiao W, Yao S, Mei W, Chen X, Luo A, Sun L, Cook T, Behringer E, Huitink JM, Wong DT, Lane-Fall M, McNarry AF, McGuire B, Higgs A, Shah A, Patel A, Zuo M, Ma W, Xue Z, Zhang LM, Li W, Wang Y, Hagberg C, O'Sullivan EP, Fleisher LA, Wei H; collaborators. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. *Br J Anaesth* 2020; **125**: e28-e37 [PMID: 32312571 DOI: 10.1016/j.bja.2020.03.026]
42 **Jain NK**, Tirupati R, Palabindala V. COVID-19: Managing resource crunch and ethical challenges. The Hospitalist: Society of Hospital Medicine, 2020. [cited 16 January 2021]. Available from: https://www.the-hospitalist.org/hospitalist/article/220724/coronavirus-updates/covid-19-managing-resource-crunch-and-ethical
43 **Tan KS**, Halpern NA. United States Resource Availability for COVID-19. In: Neil A. Halpern M, MCCM, editor: Society of Critical care Medicine, 5/12/2020. [cited 16 January 2021]. Available from: https://www.sccm.org/Blog/March-2020/United-States-Resource-Availability-for-COVID-19?_zs=jxpjd1&_zl=w9pb6
44 **Matta A**, Chaudhary S, Bryan Lo K, DeJoy R 3rd, Gul F, Torres R, Chaisson N, Patarroyo-Aponte G. Timing of Intubation and Its Implications on Outcomes in Critically Ill Patients With Coronavirus Disease 2019 Infection. *Crit Care Explor* 2020; **2**: e0262 [PMID: 33134950 DOI: 10.1097/CCE.0000000000000262]
45 **Pandya A**, Kaur NA, Sacher D, O'Corragain O, Salerno D, Desai P, Sehgal S, Gordon M, Gupta R, Marchetti N, Zhao H, Patlakh N, Criner GJ, University T; COVID-19 Research Group. Ventilatory Mechanics in Early vs Late Intubation in a Cohort of Coronavirus Disease 2019 Patients With ARDS: A Single Center's Experience. *Chest* 2021; **159**: 653-656 [PMID: 32882246 DOI: 10.1016/j.chest.2020.08.2084]
46 **Siempos II**, Xourgia E, Ntaidou TK, Zervakis D, Magira EE, Kotanidou A, Routsi C, Zakynthinos SG. Effect of Early vs. Delayed or No Intubation on Clinical Outcomes of Patients With COVID-19: An Observational Study. *Front Med (Lausanne)* 2020; **7**: 614152 [PMID: 33425957 DOI: 10.3389/fmed.2020.614152]
47 **Lee YH**, Choi KJ, Choi SH, Lee SY, Kim KC, Kim EJ, Lee J. Clinical Significance of Timing of Intubation in Critically Ill Patients with COVID-19: A Multi-Center Retrospective Study. *J Clin Med* 2020; **9** [PMID: 32887462 DOI: 10.3390/jcm9092847]
48 **Gattinoni L**, Marini JJ, Camporota L. Reply to Tobin *et al.*: Respiratory Drive Measurements Do Not Signify Conjectural Patient Self-inflicted Lung Injury. *Am J Respir Crit Care Med* 2021; **203**: 143-144 [PMID: 33064951 DOI: 10.1164/rccm.202009-3692LE]
49 **Fink JB**, Ehrmann S, Li J, Dailey P, McKiernan P, Darquenne C, Martin AR, Rothen-Rutishauser B, Kuehl PJ, Häussermann S, MacLoughlin R, Smaldone GC, Muellinger B, Corcoran TE, Dhand R. Reducing Aerosol-Related Risk of Transmission in the Era of COVID-19: An Interim Guidance Endorsed by the International Society of Aerosols in Medicine. *J Aerosol Med Pulm Drug Deliv* 2020; **33**: 300-304 [PMID: 32783675 DOI: 10.1089/jamp.2020.1615]
50 **National Asthma Council**. Managing asthma during the COVID-19 (SARS-CoV-2) pandemic. [cited 23 August 2020]. Available from: https://www.asthmahandbook.org.au/clinical-issues/covid-19
51 **al HKRPe**. Global initiative for Asthma 2020 full report, 2020. [cited 23 January 2021]. Available from: https://ginasthma.org/
52 **NICE**. COVID-19 rapid guideline: severe asthma. UK: National institute of Clinical Excellence,

United Kingdom, 04/03/2020. [cited 23 January 2021]. Available from: https://www.nice.org.uk/guidance/ng166

53 **Cazzola M**, Ora J, Bianco A, Rogliani P, Matera MG. Guidance on nebulization during the current COVID-19 pandemic. *Respir Med* 2021; **176**: 106236 [PMID: 33248363 DOI: 10.1016/j.rmed.2020.106236]

54 **Lentz RJ**, Colt H. Summarizing societal guidelines regarding bronchoscopy during the COVID-19 pandemic. *Respirology* 2020; **25**: 574-577 [PMID: 32277733 DOI: 10.1111/resp.13824]

55 **Vergnon JM**, Trosini-Desert V, Fournier C, Lachkar S, Dutau H, Guibert N, Escarguel B, Froudarakis M; French-Speaking Group on Thoracic Endoscopy (Groupe d'endoscopie de langue française GELF) of the French Language Respiratory Society (Société de pneumologie de langue française, SPLF). Bronchoscopy use in the COVID-19 era. *Respir Med Res* 2020; **78**: 100760 [PMID: 32474396 DOI: 10.1016/j.resmer.2020.100760]

56 **Chang SH**, Jiang J, Kon ZN, Williams DM, Geraci TC, Smith DE, Cerfolio RJ, Zervos M, Bizekis C. Safety and Efficacy of Bronchoscopy in Critically Ill Patients With Coronavirus Disease 2019. *Chest* 2021; **159**: 870-872 [PMID: 33039461 DOI: 10.1016/j.chest.2020.09.263]

57 **Torrego A**, Pajares V, Fernández-Arias C, Vera P, Mancebo J. Bronchoscopy in Patients with COVID-19 with Invasive Mechanical Ventilation: A Single-Center Experience. *Am J Respir Crit Care Med* 2020; **202**: 284-287 [PMID: 32412787 DOI: 10.1164/rccm.202004-0945LE]

58 **Chiesa-Estomba CM**, Lechien JR, Calvo-Henríquez C, Fakhry N, Karkos PD, Peer S, Sistiaga-Suarez JA, Gónzalez-García JA, Cammaroto G, Mayo-Yánez M, Parente-Arias P, Saussez S, Ayad T. Systematic review of international guidelines for tracheostomy in COVID-19 patients. *Oral Oncol* 2020; **108**: 104844 [PMID: 32526655 DOI: 10.1016/j.oraloncology.2020.104844]

59 **McGrath BA**, Brenner MJ, Warrillow SJ, Pandian V, Arora A, Cameron TS, Añon JM, Hernández Martínez G, Truog RD, Block SD, Lui GCY, McDonald C, Rassekh CH, Atkins J, Qiang L, Vergez S, Dulguerov P, Zenk J, Antonelli M, Pelosi P, Walsh BK, Ward E, Shang Y, Gasparini S, Donati A, Singer M, Openshaw PJM, Tolley N, Markel H, Feller-Kopman DJ. Tracheostomy in the COVID-19 era: global and multidisciplinary guidance. *Lancet Respir Med* 2020; **8**: 717-725 [PMID: 32422180 DOI: 10.1016/S2213-2600(20)30230-7]

60 **Mattioli F**, Fermi M, Ghirelli M, Molteni G, Sgarbi N, Bertellini E, Girardis M, Presutti L, Marudi A. Tracheostomy in the COVID-19 pandemic. *Eur Arch Otorhinolaryngol* 2020; **277**: 2133-2135 [PMID: 32322959 DOI: 10.1007/s00405-020-05982-0]

61 **Kwak PE**, Connors JR, Benedict PA, Timen MR, Wang B, Zhang Y, Youlios S, Sureau K, Persky MJ, Rafeq S, Angel L, Amin MR. Early Outcomes From Early Tracheostomy for Patients With COVID-19. *JAMA Otolaryngol Head Neck Surg* 2021; **147**: 239-244 [PMID: 33331855 DOI: 10.1001/jamaoto.2020.4837]

62 **Queen Elizabeth Hospital Birmingham COVID-19 airway team**. Safety and 30-day outcomes of tracheostomy for COVID-19: a prospective observational cohort study. *Br J Anaesth* 2020; **125**: 872-879 [PMID: 32988602 DOI: 10.1016/j.bja.2020.08.023]

63 **Mattioli F**, Marudi A, Ghirelli M, Molteni G, Sgarbi N, Valerini S, Girardis M, Presutti L, Fermi M. Reply to "Indications and timing for tracheostomy in patients with SARS CoV2-related" by Ferri *et al*. *Eur Arch Otorhinolaryngol* 2020; **277**: 2405-2406 [PMID: 32556782 DOI: 10.1007/s00405-020-06134-0]

64 **McGrath BA**, Brenner MJ, Warrillow SJ. Tracheostomy for COVID-19: business as usual? *Br J Anaesth* 2020; **125**: 867-871 [PMID: 32951840 DOI: 10.1016/j.bja.2020.08.048]

65 **Benito DA**, Bestourous DE, Tong JY, Pasick LJ, Sataloff RT. Tracheotomy in COVID-19 Patients: A Systematic Review and Meta-analysis of Weaning, Decannulation, and Survival. *Otolaryngol Head Neck Surg* 2021; 194599820984780 [PMID: 33399526 DOI: 10.1177/0194599820984780]

66 **Marano G**, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, Grazzini G. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus* 2016; **14**: 152-157 [PMID: 26674811 DOI: 10.2450/2015.0131-15]

67 **Winkler AM**, Koepsell SA. The use of convalescent plasma to treat emerging infectious diseases: focus on Ebola virus disease. *Curr Opin Hematol* 2015; **22**: 521-526 [PMID: 26457963 DOI: 10.1097/MOH.0000000000000191]

68 **Jiang S**, Zhang X, Yang Y, Hotez PJ, Du L. Neutralizing antibodies for the treatment of COVID-19. *Nat Biomed Eng* 2020; **4**: 1134-1139 [PMID: 33293725 DOI: 10.1038/s41551-020-00660-2]

69 **Nguyen AA**, Habiballah SB, Platt CD, Geha RS, Chou JS, McDonald DR. Immunoglobulins in the treatment of COVID-19 infection: Proceed with caution! *Clin Immunol* 2020; **216**: 108459 [PMID: 32418917 DOI: 10.1016/j.clim.2020.108459]

70 **Joyner MJ**, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Diaz Soto JC, Baker SE, Shepherd JRA, van Helmond N, Verdun NC, Marks P, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whelan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather D, Wright RS, Casadevall A. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. *N Engl J Med* 2021; **384**: 1015-1027 [PMID: 33523609 DOI: 10.1056/NEJMoa2031893]

71 **Li L**, Zhang W, Hu Y, Tong X, Zheng S, Yang J, Kong Y, Ren L, Wei Q, Mei H, Hu C, Tao C, Yang R, Wang J, Yu Y, Guo Y, Wu X, Xu Z, Zeng L, Xiong N, Chen L, Man N, Liu Y, Xu H, Deng E, Zhang X, Li C, Wang C, Su S, Zhang L, Wu Y, Liu Z. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A

Randomized Clinical Trial. *JAMA* 2020; **324**: 460-470 [PMID: 32492084 DOI: 10.1001/jama.2020.10044]

72 **Agarwal A**, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P; PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020; **371**: m3939 [PMID: 33093056 DOI: 10.1136/bmj.m3939]

73 **Simonovich VA**, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, Savoy N, Giunta DH, Pérez LG, Sánchez MDL, Gamarnik AV, Ojeda DS, Santoro DM, Camino PJ, Antelo S, Rainero K, Vidiella GP, Miyazaki EA, Cornistein W, Trabadelo OA, Ross FM, Spotti M, Funtowicz G, Scordo WE, Losso MH, Ferniot I, Pardo PE, Rodriguez E, Rucci P, Pasquali J, Fuentes NA, Esperatti M, Speroni GA, Nannini EC, Matteaccio A, Michelangelo HG, Follmann D, Lane HC, Belloso WH; PlasmAr Study Group. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. *N Engl J Med* 2021; **384**: 619-629 [PMID: 33232588 DOI: 10.1056/NEJMoa2031304]

74 **Libster R**, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, Esteban I, Caballero MT, Wood C, Berrueta M, Rondan A, Lescano G, Cruz P, Ritou Y, Fernández Viña V, Álvarez Paggi D, Esperante S, Ferreti A, Ofman G, Ciganda Á, Rodriguez R, Lantos J, Valentini R, Itcovici N, Hintze A, Oyarvide ML, Etchegaray C, Neira A, Name I, Alfonso J, López Castelo R, Caruso G, Rapelius S, Alvez F, Etchenique F, Dimase F, Alvarez D, Aranda SS, Sánchez Yanotti C, De Luca J, Jares Baglivo S, Laudanno S, Nowogrodzki F, Larrea R, Silveyra M, Leberzstein G, Debonis A, Molinos J, González M, Perez E, Kreplak N, Pastor Argüello S, Gibbons L, Althabe F, Bergel E, Polack FP; Fundación INFANT–COVID-19 Group. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. *N Engl J Med* 2021; **384**: 610-618 [PMID: 33406353 DOI: 10.1056/NEJMoa2033700]

75 **FDA**. US Food and Drug Administration RDMH. FDA, 2021. [cited 23 January 2021]. Available from: https://www.fda.gov/

76 **Bloch EM**, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, van Buskirk C, Grossman BJ, Joyner M, Henderson JP, Pekosz A, Lau B, Wesolowski A, Katz L, Shan H, Auwaerter PG, Thomas D, Sullivan DJ, Paneth N, Gehrie E, Spitalnik S, Hod EA, Pollack L, Nicholson WT, Pirofski LA, Bailey JA, Tobian AA. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest* 2020; **130**: 2757-2765 [PMID: 32254064 DOI: 10.1172/JCI138745]

77 EUA for Bamlanivimab-A Monoclonal Antibody for COVID-19. *JAMA* 2021; **325**: 880-881 [PMID: 33306087 DOI: 10.1001/jama.2020.24415]

78 **Company ELa**. Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents. 2021. [cited 23 January 2021]. Available from: https://www.prnewswire.com/news-releases/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented-covid-19-at-nursing-homes-in-the-blaze-2-trial-reducing-risk-by-up-to-80-percent-for-residents-301212159.html

79 **Hinton RDM**, Scientist C, Administration FaD. USA: FDA, 2021. [cited 23 January 2021]. Available from: https://www.fda.gov/home

80 **Horby PW**, Estcourt L, Peto L, Emberson JR, Staplin N, Spata E, Pessoa-Amorim G, Campbell M, Roddick A, Brunskill NE, George T, Zehnder D, Tiberi S, Aung NN, Uriel A, Widdrington J, Koshy G, Brown T, Scott S, Baillie JK, Buch MH, Chappell LC, Day JN, Faust SN, Jaki T, Jeffery K, Juszczak E, Lim WS, Montgomery A, Mumford A, Rowan K, Thwaites G, Mafham M, Roberts D, Haynes R, Landray MJ. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. 2021 Preprint. Available from: medRxiv: 2021: 2021.2003.2009.21252736

81 **Strehl C**, Ehlers L, Gaber T, Buttgereit F. Glucocorticoids-All-Rounders Tackling the Versatile Players of the Immune System. *Front Immunol* 2019; **10**: 1744 [PMID: 31396235 DOI: 10.3389/fimmu.2019.01744]

82 **RECOVERY Collaborative Group**. , Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]

83 **Siemieniuk RA**, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, Pardo-Hernandez H, Rochwerg B, Lamontagne F, Han MA, Liu Q, Agarwal A, Agoritsas T, Chu DK, Couban R, Darzi A, Devji T, Fang B, Fang C, Flottorp SA, Foroutan F, Ghadimi M, Heels-Ansdell D, Honarmand K, Hou L, Hou X, Ibrahim Q, Khamis A, Lam B, Loeb M, Marcucci M, McLeod SL, Motaghi S, Murthy S, Mustafa RA, Neary JD, Qasim A, Rada G, Riaz IB, Sadeghirad B, Sekercioglu N, Sheng L, Sreekanta A, Switzer C, Tendal B, Thabane L, Tomlinson G, Turner T, Vandvik PO, Vernooij RW, Viteri-García A, Wang Y, Yao L, Ye Z, Guyatt GH, Brignardello-Petersen R, Martinez JPD, Cusano E. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020; **370**: m2980 [PMID: 32732190 DOI: 10.1136/bmj.m2980]

84 **INC AP**. Alexion Provides Update on Phase 3 Study of ULTOMIRIS® (ravulizumab-cwvz) in Hospitalized Patients with Severe COVID-19. 2021. [cited 23 January 2021]. Available from: https://pipelinereview.com/index.php/2021011477170/Antibodies/Alexion-Provides-Update-on-Phase-3-Study-of-ULTOMIRIS-ravulizumab-cwvz-in-Hospitalized-Patients-with-Severe-COVID-19.html

85 **Parr JB**. Time to Reassess Tocilizumab's Role in COVID-19 Pneumonia. *JAMA Intern Med* 2021; **181**: 12-15 [PMID: 33079980 DOI: 10.1001/jamainternmed.2020.6557]

86 **Gordon AC**, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley D, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettilä V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. 2021 Preprint. Available from: medRxiv: 2021: 2021.2001.2007.21249390

87 Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, Lorenzi E, Marshall JC, Mayr FB, McAuley DF, McGlothlin A, McGuinness SP, McVerry BJ, Montgomery SK, Morpeth SC, Murthy S, Orr K, Parke RL, Parker JC, Patanwala AE, Pettilä V, Rademaker E, Santos MS, Saunders CT, Seymour CW, Shankar-Hari M, Sligl WI, Turgeon AF, Turner AM, van de Veerdonk FL, Zarychanski R, Green C, Lewis RJ, Angus DC, McArthur CJ, Berry S, Webb SA, Derde LPG. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med* 2021; **384:** 1491-1502. [PMID: 33631065 DOI: 10.1056/NEJMoa2100433]

88 **Horby PW**, Campbell M, Staplin N, Spata E, Emberson JR, Pessoa-Amorim G, Peto L, Brightling CE, Sarkar R, Thomas K, Jeebun V, Ashish A, Tully R, Chadwick D, Sharafat M, Stewart R, Rudran B, Baillie JK, Buch MH, Chappell LC, Day JN, Furst SN, Jaki T, Jeffery K, Juszczak E, Lim WS, Montgomery A, Mumford A, Rowan K, Thwaites G, Mafham M, Haynes R, Landray MJ. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. 2021 Preprint. Available from: medRxiv 2021: 2021.2002.2011.21249258

89 **Gupta S**, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, Reiser J, Bansal A, Srivastava A, Zhou Y, Finkel D, Green A, Mallappallil M, Faugno AJ, Zhang J, Velez JCQ, Shaefi S, Parikh CR, Charytan DM, Athavale AM, Friedman AN, Redfern RE, Short SAP, Correa S, Pokharel KK, Admon AJ, Donnelly JP, Gershengorn HB, Douin DJ, Semler MW, Hernán MA, Leaf DE; STOP-COVID Investigators. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. *JAMA Intern Med* 2021; **181**: 41-51 [PMID: 33080002 DOI: 10.1001/jamainternmed.2020.6252]

90 **Government U**. Thousands more NHS patients to get life-saving COVID-19 treatment. 2021. [cited 23 January 2021]. Available from: https://www.nhs.uk/conditions/coronavirus-covid-19/

91 **CDC**. CDC Treatment guidelines for Covid-19. 2021. [cited 23 January 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/index.html

92 **Beigel JH**, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh MD, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC; ACTT-1 Study Group Members. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020; **383**: 1813-1826 [PMID: 32445440 DOI: 10.1056/NEJMoa2007764]

93 **Wang Y**, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; **395**: 1569-1578 [PMID: 32423584 DOI: 10.1016/S0140-6736(20)31022-9]

94 **WHO Solidarity Trial Consortium**. , Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med* 2021; **384**: 497-511 [PMID: 33264556 DOI: 10.1056/NEJMoa2023184]

95 **Veiga VC**, Prats JAGG, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, Machado FR, Lopes RD, Berwanger O, Azevedo LCP, Avezum Á, Lisboa TC, Rojas SSO, Coelho JC, Leite RT, Carvalho JC, Andrade LEC, Sandes AF, Pintão MCT, Castro CG, Santos SV, de Almeida TML,

Costa AN, Gebara OCE, de Freitas FGR, Pacheco ES, Machado DJB, Martin J, Conceição FG, Siqueira SRR, Damiani LP, Ishihara LM, Schneider D, de Souza D, Cavalcanti AB, Scheinberg P. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ* 2021; **372**: n84 [PMID: 33472855 DOI: 10.1136/bmj.n84]

96 **Spinner CD**, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, Ogbuagu O, Malhotra P, Mullane KM, Castagna A, Chai LYA, Roestenberg M, Tsang OTY, Bernasconi E, Le Turnier P, Chang SC, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wang H, Gaggar A, Brainard DM, McPhail MJ, Bhagani S, Ahn MY, Sanyal AJ, Huhn G, Marty FM; GS-US-540-5774 Investigators. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA* 2020; **324**: 1048-1057 [PMID: 32821939 DOI: 10.1001/jama.2020.16349]

97 **Goldman JD**, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, Chen YS, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A; GS-US-540-5773 Investigators. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med* 2020; **383**: 1827-1837 [PMID: 32459919 DOI: 10.1056/NEJMoa2015301]

98 **Kalil AC**, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, Marconi VC, Ruiz-Palacios GM, Hsieh L, Kline S, Tapson V, Iovine NM, Jain MK, Sweeney DA, El Sahly HM, Branche AR, Regalado Pineda J, Lye DC, Sandkovsky U, Luetkemeyer AF, Cohen SH, Finberg RW, Jackson PEH, Taiwo B, Paules CI, Arguinchona H, Erdmann N, Ahuja N, Frank M, Oh MD, Kim ES, Tan SY, Mularski RA, Nielsen H, Ponce PO, Taylor BS, Larson L, Rouphael NG, Saklawi Y, Cantos VD, Ko ER, Engemann JJ, Amin AN, Watanabe M, Billings J, Elie MC, Davey RT, Burgess TH, Ferreira J, Green M, Makowski M, Cardoso A, de Bono S, Bonnett T, Proschan M, Deye GA, Dempsey W, Nayak SU, Dodd LE, Beigel JH; ACTT-2 Study Group Members. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med* 2021; **384**: 795-807 [PMID: 33306283 DOI: 10.1056/NEJMoa2031994]

99 **Bartoszko JJ**, Siemieniuk RAC, Kum E, Qasim A, Zeraatkar D, Ge L, Han MA, Sadeghirad B, Agarwal A, Agoritsas T, Chu DK, Couban R, Darzi AJ, Devji T, Ghadimi M, Honarmand K, Izcovich A, Khamis A, Lamontagne F, Loeb M, Marcucci M, McLeod SL, Motaghi S, Murthy S, Mustafa RA, Neary JD, Pardo-Hernandez H, Rada G, Rochwerg B, Switzer C, Tendal B, Thabane L, Vandvik PO, Vernooij RWM, Viteri-García A, Wang Y, Yao L, Ye Z, Guyatt GH, Brignardello-Petersen R. Prophylaxis against covid-19: living systematic review and network meta-analysis. *BMJ* 2021; **373**: n949 [PMID: 33903131 DOI: 10.1136/bmj.n949]

100 **Young B**, Tan TT, Leo YS. The place for remdesivir in COVID-19 treatment. *Lancet Infect Dis* 2021; **21**: 20-21 [PMID: 33248473 DOI: 10.1016/S1473-3099(20)30911-7]

101 **Kaka AS**, MacDonald R, Greer N, Vela K, Duan-Porter W, Obley A, Wilt TJ. Major Update: Remdesivir for Adults With COVID-19: A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points. *Ann Intern Med* 2021 [PMID: 33560863 DOI: 10.7326/M20-8148]

102 **Dyer O**. Covid-19: Remdesivir has little or no impact on survival, WHO trial shows. *BMJ* 2020; **371**: m4057 [PMID: 33077424 DOI: 10.1136/bmj.m4057]

103 **Harrington DP**, Baden LR, Hogan JW. A Large, Simple Trial Leading to Complex Questions. *N Engl J Med* 2021; **384**: 576-577 [PMID: 33264557 DOI: 10.1056/NEJMe2034294]

104 **Ghazy RM**, Almaghraby A, Shaaban R, Kamal A, Beshir H, Moursi A, Ramadan A, Taha SHN. A systematic review and meta-analysis on chloroquine and hydroxychloroquine as monotherapy or combined with azithromycin in COVID-19 treatment. *Sci Rep* 2020; **10**: 22139 [PMID: 33335141 DOI: 10.1038/s41598-020-77748-x]

105 **Self WH**, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, Chang SY, Collins SP, Eppensteiner JC, Filbin MR, Files DC, Gibbs KW, Ginde AA, Gong MN, Harrell FE Jr, Hayden DL, Hough CL, Johnson NJ, Khan A, Lindsell CJ, Matthay MA, Moss M, Park PK, Rice TW, Robinson BRH, Schoenfeld DA, Shapiro NI, Steingrub JS, Ulysse CA, Weissman A, Yealy DM, Thompson BT, Brown SM; National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Steingrub J, Smithline H, Tiru B, Tidswell M, Kozikowski L, Thornton-Thompson S, De Souza L, Hou P, Baron R, Massaro A, Aisiku I, Fredenburgh L, Seethala R, Johnsky L, Riker R, Seder D, May T, Baumann M, Eldridge A, Lord C, Shapiro N, Talmor D, O'Mara T, Kirk C, Harrison K, Kurt L, Schermerhorn M, Banner-Goodspeed V, Boyle K, Dubosh N, Filbin M, Hibbert K, Parry B, Lavin-Parsons K, Pulido N, Lilley B, Lodenstein C, Margolin J, Brait K, Jones A, Galbraith J, Peacock R, Nandi U, Wachs T, Matthay M, Liu K, Kangelaris K, Wang R, Calfee C, Yee K, Hendey G, Chang S, Lim G, Qadir N, Tam A, Beutler R, Levitt J, Wilson J, Rogers A, Vojnik R, Roque J, Albertson T, Chenoweth J, Adams J, Pearson S, Juarez M, Almasri E, Fayed M, Hughes A, Hillard S, Huebinger R, Wang H, Vidales E, Patel B, Ginde A, Baduashvili A, McKeehan J, Finck L, Higgins C, Howell M, Douglas I, Haukoos J, Hiller T, Lyle C, Cupelo A, Caruso E, Camacho C, Gravitz S, Finigan J, Griesmer C, Park P, Hyzy R, Nelson K, McDonough K, Olbrich N, Williams M, Kapoor R, Nash J, Willig M, Ford H, Gardner-Gray J, Ramesh M, Moses M, Ng Gong M, Aboodi M, Asghar A, Amosu O, Torres M, Kaur S, Chen JT, Hope A, Lopez B, Rosales K, Young You J, Mosier J, Hypes C, Natt B, Borg B, Salvagio Campbell E, Hite RD, Hudock K, Cresie A, Alhasan F, Gomez-Arroyo J, Duggal A, Mehkri O, Hastings A, Sahoo D, Abi Fadel F, Gole S,

Shaner V, Wimer A, Meli Y, King A, Terndrup T, Exline M, Pannu S, Robart E, Karow S, Hough C, Robinson B, Johnson N, Henning D, Campo M, Gundel S, Seghal S, Katsandres S, Dean S, Krol O, Jouzestani M, Huynh P, Yealy D, Scholl D, Adams P, McVerry B, Huang D, Angus D, Schooler J, Moore S, Files C, Miller C, Gibbs K, LaRose M, Flores L, Koehler L, Morse C, Sanders J, Langford C, Nanney K, MdalaGausi M, Yeboah P, Morris P, Sturgill J, Seif S, Cassity E, Dhar S, de Wit M, Mason J, Goodwin A, Hall G, Grady A, Chamberlain A, Brown S, Bledsoe J, Leither L, Peltan I, Starr N, Fergus M, Aston V, Montgomery Q, Smith R, Merrill M, Brown K, Armbruster B, Harris E, Middleton E, Paine R, Johnson S, Barrios M, Eppensteiner J, Limkakeng A, McGowan L, Porter T, Bouffler A, Leahy JC, deBoisblanc B, Lammi M, Happel K, Lauto P, Self W, Casey J, Semler M, Collins S, Harrell F, Lindsell C, Rice T, Stubblefield W, Gray C, Johnson J, Roth M, Hays M, Torr D, Zakaria A, Schoenfeld D, Thompson T, Hayden D, Ringwood N, Oldmixon C, Ulysse C, Morse R, Muzikansky A, Fitzgerald L, Whitaker S, Lagakos A, Brower R, Reineck L, Aggarwal N, Bienstock K, Freemer M, Maclawiw M, Weinmann G, Morrison L, Gillespie M, Kryscio R, Brodie D, Zareba W, Rompalo A, Boeckh M, Parsons P, Christie J, Hall J, Horton N, Zoloth L, Dickert N, Diercks D. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. *JAMA* 2020; **324**: 2165-2176 [PMID: 33165621 DOI: 10.1001/jama.2020.22240]

106 **Borba MGS**, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, Mourão MPG, Brito-Sousa JD, Baía-da-Silva D, Guerra MVF, Hajjar LA, Pinto RC, Balieiro AAS, Pacheco AGF, Santos JDO Jr, Naveca FG, Xavier MS, Siqueira AM, Schwarzbold A, Croda J, Nogueira ML, Romero GAS, Bassat Q, Fontes CJ, Albuquerque BC, Daniel-Ribeiro CT, Monteiro WM, Lacerda MVG; CloroCovid-19 Team. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. *JAMA Netw Open* 2020; **3**: e208857 [PMID: 32330277 DOI: 10.1001/jamanetworkopen.2020.8857]

107 **Shekar K**, Badulak J, Peek G, Boeken U, Dalton HJ, Arora L, Zakhary B, Ramanathan K, Starr J, Akkanti B, Antonini MV, Ogino MT, Raman L, Barret N, Brodie D, Combes A, Lorusso R, MacLaren G, Müller T, Paden M, Pellegrino V; ELSO Guideline Working Group. Extracorporeal Life Support Organization Coronavirus Disease 2019 Interim Guidelines: A Consensus Document from an International Group of Interdisciplinary Extracorporeal Membrane Oxygenation Providers. *ASAIO J* 2020; **66**: 707-721 [PMID: 32604322 DOI: 10.1097/MAT.0000000000001193]

108 **Zangrillo A**, Biondi-Zoccai G, Landoni G, Frati G, Patroniti N, Pesenti A, Pappalardo F. Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: a systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO. *Crit Care* 2013; **17**: R30 [PMID: 23406535 DOI: 10.1186/cc12512]

109 **Barbaro RP**, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, Bartlett RH, Tonna JE, Hyslop R, Fanning JJ, Rycus PT, Hyer SJ, Anders MM, Agerstrand CL, Hryniewicz K, Diaz R, Lorusso R, Combes A, Brodie D; Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet* 2020; **396**: 1071-1078 [PMID: 32987008 DOI: 10.1016/S0140-6736(20)32008-0]

110 **Haiduc AA**, Alom S, Melamed N, Harky A. Role of extracorporeal membrane oxygenation in COVID-19: A systematic review. *J Card Surg* 2020; **35**: 2679-2687 [PMID: 32717771 DOI: 10.1111/jocs.14879]

111 **Hechanova LA**. Texas Tech University. Merck Manual Professional version. USA: Merck Manual, December 2020. [cited 16 January 2021]. Available from: https://www.merckmanuals.com/professional/

112 **Ostermann M**, Lumlertgul N, Forni LG, Hoste E. What every Intensivist should know about COVID-19 associated acute kidney injury. *J Crit Care* 2020; **60**: 91-95 [PMID: 32777758 DOI: 10.1016/j.jcrc.2020.07.023]

113 **Raza A**, Estepa A, Chan V, Jafar MS. Acute Renal Failure in Critically Ill COVID-19 Patients With a Focus on the Role of Renal Replacement Therapy: A Review of What We Know So Far. *Cureus* 2020; **12**: e8429 [PMID: 32642345 DOI: 10.7759/cureus.8429]

114 **Adapa S**, Aeddula NR, Konala VM, Chenna A, Naramala S, Madhira BR, Gayam V, Balla M, Muppidi V, Bose S. COVID-19 and Renal Failure: Challenges in the Delivery of Renal Replacement Therapy. *J Clin Med Res* 2020; **12**: 276-285 [PMID: 32489502 DOI: 10.14740/jocmr4160]

115 **Shankaranarayanan D**, Muthukumar T, Barbar T, Bhasin A, Gerardine S, Lamba P, Leuprecht L, Neupane SP, Salinas T, Shimonov D, Varma E, Liu F. Anticoagulation Strategies and Filter Life in COVID-19 Patients Receiving Continuous Renal Replacement Therapy: A Single-Center Experience. *Clin J Am Soc Nephrol* 2020; **16**: 124-126 [PMID: 32943397 DOI: 10.2215/CJN.08430520]

116 **Nadim MK**, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M, Rimmelé T, Zarbock A, Bell S, Bihorac A, Cantaluppi V, Hoste E, Husain-Syed F, Germain MJ, Goldstein SL, Gupta S, Joannidis M, Kashani K, Koyner JL, Legrand M, Lumlertgul N, Mohan S, Pannu N, Peng Z, Perez-Fernandez XL, Pickkers P, Prowle J, Reis T, Srisawat N, Tolwani A, Vijayan A, Villa G, Yang L, Ronco C, Kellum JA. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. *Nat Rev Nephrol* 2020; **16**: 747-764 [PMID: 33060844 DOI: 10.1038/s41581-020-00356-5]

117 **Ronco C**, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat*

Rev Nephrol 2020; **16**: 308-310 [PMID: 32273593 DOI: 10.1038/s41581-020-0284-7]

118 **Yang X**, Tian S, Guo H. Acute kidney injury and renal replacement therapy in COVID-19 patients: A systematic review and meta-analysis. *Int Immunopharmacol* 2021; **90**: 107159 [PMID: 33223467 DOI: 10.1016/j.intimp.2020.107159]

119 **Walkey AJ**, Kumar VK, Harhay MO, Bolesta S, Bansal V, Gajic O, Kashyap R. The Viral Infection and Respiratory Illness Universal Study (VIRUS): An International Registry of Coronavirus 2019-Related Critical Illness. *Crit Care Explor* 2020; **2**: e0113 [PMID: 32426754 DOI: 10.1097/CCE.0000000000000113]

120 **Walkey AJ**, Sheldrick RC, Kashyap R, Kumar VK, Boman K, Bolesta S, Zampieri FG, Bansal V, Harhay MO, Gajic O. Guiding Principles for the Conduct of Observational Critical Care Research for Coronavirus Disease 2019 Pandemics and Beyond: The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med* 2020; **48**: e1038-e1044 [PMID: 32932348 DOI: 10.1097/CCM.0000000000004572]

121 **Domecq JP**, Lal A, Sheldrick CR, Kumar VK, Boman K, Bolesta S, Bansal V, Harhay MO, Garcia MA, Kaufman M, Danesh V, Cheruku S, Banner-Goodspeed VM, Anderson HL 3rd, Milligan PS, Denson JL, St Hill CA, Dodd KW, Martin GS, Gajic O, Walkey AJ, Kashyap R. Outcomes of Patients With Coronavirus Disease 2019 Receiving Organ Support Therapies: The International Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med* 2021; **49**: 437-448 [PMID: 33555777 DOI: 10.1097/CCM.0000000000004879]

122 **Anesi GL**, Jablonski J, Harhay MO, Atkins JH, Bajaj J, Baston C, Brennan PJ, Candeloro CL, Catalano LM, Cereda MF, Chandler JM, Christie JD, Collins T, Courtright KR, Fuchs BD, Gordon E, Greenwood JC, Gudowski S, Hanish A, Hanson Iii CW, Heuer M, Kinniry P, Kornfield ZN, Kruse GB, Lane-Fall M, Martin ND, Mikkelsen ME, Negoianu D, Pascual JL, Patel MB, Pugliese SC, Qasim ZA, Reilly JP, Salmon J, Schweickert WD, Scott MJ, Shashaty MGS, Sicoutris CP, Wang JK, Wang W, Wani AA, Anderson BJ, Gutsche JT. Characteristics, Outcomes, and Trends of Patients With COVID-19-Related Critical Illness at a Learning Health System in the United States. *Ann Intern Med* 2021 [PMID: 33460330 DOI: 10.7326/M20-5327]

123 **Bravata DM**, Perkins AJ, Myers LJ, Arling G, Zhang Y, Zillich AJ, Reese L, Dysangco A, Agarwal R, Myers J, Austin C, Sexson A, Leonard SJ, Dev S, Keyhani S. Association of Intensive Care Unit Patient Load and Demand With Mortality Rates in US Department of Veterans Affairs Hospitals During the COVID-19 Pandemic. *JAMA Netw Open* 2021; **4**: e2034266 [PMID: 33464319 DOI: 10.1001/jamanetworkopen.2020.34266]

124 **O'Horo JC**, Cerhan JR, Cahn EJ, Bauer PR, Temesgen Z, Ebbert J, Abril A, Abu Saleh OM, Assi M, Berbari EF, Bierle DM, Bosch W, Burger CD, Cano Cevallos EJ, Clements CM, Carmona Porquera EM, Castillo Almeida NE, Challener DW, Chesdachai S, Comba IY, Corsini Campioli CG, Crane SJ, Dababneh AS, Enzler MJ, Fadel HJ, Ganesh R, De Moraes AG, Go JR, Gordon JE, Gurram PR, Guru PK, Halverson EL, Harrison MF, Heaton HA, Hurt R, Kasten MJ, Lee AS, Levy ER, Libertin CR, Mallea JM, Marshall WF, Matcha G, Meehan AM, Franco PM, Morice WG, O'Brien JJ, Oeckler R, Ommen S, Oravec CP, Orenstein R, Ough NJ, Palraj R, Patel BM, Pureza VS, Pickering B, Phelan DM, Razonable RR, Rizza S, Sampathkumar P, Sanghavi DK, Sen A, Siegel JL, Singbartl K, Shah AS, Shweta FNU, Speicher LL, Suh G, Tabaja H, Tande A, Ting HH, Tontz RC, Vaillant JJ, Vergidis P, Warsame MY, Yetmar ZA, Zomok CD, Williams AW, Badley AD. Outcomes of COVID-19 With the Mayo Clinic Model of Care and Research. *Mayo Clin Proc* 2021; **96**: 601-618 [PMID: 33673913 DOI: 10.1016/j.mayocp.2020.12.006]

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MINIREVIEWS

Glucocorticoid and mineralocorticoid receptor expression in critical illness: A narrative review

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Abstract

The glucocorticoid receptor (GCR) and the mineralocorticoid receptor (MR) are members of the steroid receptor superfamily of hormone-dependent transcription factors. The receptors are structurally and functionally related. They are localized in the cytosol and translocate into the nucleus after ligand binding. GCRs and MRs can be co-expressed within the same cell, and it is believed that the balance in GCR and MR expression is crucial for homeostasis and plays a key role in normal adaptation. In critical illness, the hypothalamic-pituitary-adrenal axis is activated, and as a consequence, serum cortisol concentrations are high. However, a number of patients exhibit relatively low cortisol levels for the degree of illness severity. Glucocorticoid (GC) actions are facilitated by GCR, whose dysfunction leads to GC tissue resistance. The MR is unique in this family in that it binds to both aldosterone and cortisol. Endogenous GCs play a critical role in controlling inflammatory responses in critical illness. Intracellular GC concentrations can differ greatly from blood levels due to the action of the two 11β-hydroxysteroid dehydrogenase isozymes, type 1 and type 2. 11β-hydroxysteroid dehydrogenases interconvert endogenous active cortisol and intrinsically inert cortisone. The degree of expression of the two isozymes has the potential to dramatically influence local GC availability within cells and tissues. In this review, we will explore the clinical studies that aimed to elucidate the role of MR and GCR expression in the inflammatory response seen in critical illness.

Key Words: Mineralocorticoid receptor; Glucocorticoid receptor, Critical illness; 11beta-hydroxysteroid dehydrogenase; Aldosterone; Cortisol

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Core Tip: Endogenous glucocorticoids (GCs) play a critical role in controlling inflammatory responses in critical illness. Intracellular GC concentrations can differ greatly due to the action of the two 11β-hydroxysteroid dehydrogenase isozymes. The degree of expression of the two isozymes has the potential to dramatically influence local GC availability. The GC receptor and the mineralocorticoid receptor are members of the steroid receptor superfamily of hormone-dependent transcription factors. The study of the mineralocorticoid receptor and GC receptor expression and function in the inflammatory response seen in critical illness might aid in identifying the patients who will benefit from exogenous corticosteroid administration.

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INTRODUCTION

The glucocorticoid receptor (GCR) and the mineralocorticoid receptor (MR) are members of the steroid receptor superfamily of hormone-dependent transcription factors. The receptors are structurally and functionally related. They are localized in the cytosol and translocate into the nucleus after ligand binding. GCRs and MRs can be co-expressed within the same cell, and it is believed that the balance in GCR and MR expression is crucial for homeostasis and plays a key role in normal adaptation.

In critical illness, the hypothalamic-pituitary-adrenal (HPA) axis is activated, and as a consequence, serum cortisol concentrations are high. However, in a number of patients cortisol levels are relatively low for their illness severity. Glucocorticoid (GC) actions are mediated by GCR, whose dysfunction leads to GC tissue resistance. The MR is unique in this family in that it binds to both aldosterone and cortisol.

Endogenous GCs play a critical role in controlling inflammatory responses in critical illness. Intracellular GC concentrations may be greatly different compared to blood levels due to the action of the 11β-hydroxysteroid dehydrogenase (11β-HSD) isozymes, type 1 and type 2. 11β-HSDs interconvert endogenous active cortisol and intrinsically inert cortisone. The degree of expression of the two isozymes has the potential to dramatically influence local GC availability within cells and tissues.

GCR

During critical illness the HPA axis is activated, resulting in increased serum adrenocorticotropic hormone and cortisol concentrations[1-4]. However, a subset of patients present with low serum cortisol levels despite their illness severity[5,6]. Critical illness-related corticosteroid insufficiency (CIRCI) is characterized by the organism's inability to produce adequate cortisol or tissue resistance to its actions, or both[7].

Sepsis and septic shock are the most common causes of mortality in critically-ill patients. GCs, the end-products of the HPA axis, have been used for over 40 years in the treatment of sepsis. The Surviving Sepsis Campaign Guidelines 2016 recommended hydrocortisone administration when despite adequate fluid resuscitation and vasopressor therapy, the hemodynamic stability in septic shock cannot be restored[8]. However, not all patients benefit from their administration, and as yet the patients who would benefit from their use cannot be accurately identified[9-12].

Cortisol signaling is mediated by GCR, a ubiquitous intracellular receptor protein. Alternative splicing of the primary transcript gives rise to two highly homologous GCR isoforms[13]. GCR-α is the functionally active receptor; once it binds to cortisol, the receptor-cortisol complex translocates from the cytosol to the nucleus. In the nucleus, the complex exerts transcriptional activation or repression by directly binding to genes that contain GC responsive elements[14], resulting in the inhibition of the

inflammatory response[15,16]. On the contrary, the function of GCR-β has not been well-explored. It is known to suppress GCR-α activity and is unable to bind both natural and synthetic ligands[17-19]. Figure 1 diagrammatically represents cortisol signaling *via* GCR.

The Sepsis-3 guidelines suggest the use of hydrocortisone in septic shock patients who are resistant to fluid administration and vasoactive agents[20]. Not all patients respond to this therapy, suggesting the existence of GC resistance. GC resistance is defined as the inability of GCs to exert their effects on target tissues[21]. It is characterized by decreased sensitivity of immune cells to GCs, which under normal conditions terminate the inflammatory response[22]. Therefore, it becomes apparent that apart from cortisol levels, how tissues respond to cortisol is as important. It has been suggested that the extent of cortisol's effect might be analogous to GCR expression, subtype and affinity in a specific target cell[23]. Such an example is the increased expression of *GCR-β* in certain tissues in inflammatory diseases, which has been associated with decreased sensitivity to GCs[24].

GC resistance may be a consequence of decreased *GCR* expression, GCR affinity for the ligand, nuclear translocation and DNA binding or may be due to altered transcription factor interaction. Most data on GC resistance in critical illness originates from experimental models involving sepsis-induced injury[25-29]. Essentially these studies have shown downregulation of *GCR-a* and induction of *GCR-β* expression[30-33].

Human clinical studies in critically-ill patients have mostly investigated cortisol availability, while only a few have explored the role of GCR. GC resistance has been described in a cohort of septic patients, demonstrating reduced *GCR-a* and elevated *GCR-β* expression levels in septic patients compared to healthy subjects; these results suggest that treatment with steroids might aggravate GC resistance in patients with increased GCR-β levels[34]. A transient, increased *GCR-β* expression has been reported in sepsis; moreover, the septic patients' sera could induce GC resistance *in vitro*[35]. Another study reported reduced *GCR-a* expression levels in sepsis[36], and diminished GCR protein levels have also been described in various organs during sepsis[37]. A decreased number of GCR-α and increased GCR-β receptors has been shown in heart and liver biopsies in the context of sepsis[25]. It has been shown that in septic shock, *GCR* expression increased, while GCR binding capacity decreased, proposing that it is the decreased GCR binding capacity and not the number of receptors that interferes with the response to exogenous or endogenous GCs[38]. In contrast, GCR number and affinity in septic patients did not differ from control subjects, suggesting that GCs could be effective in the hemodynamic compensatory phase of sepsis[39]. Increased *GCR-a* expression has been shown in the acute phase of sepsis, questioning the need for exogenous steroids at this phase[40]. Only one study has demonstrated downregulation of cortisol binding in critically-ill, ventilated patients[41]. Finally, our group was able to demonstrate that critically-ill steroid-free patients have a highly variable expression of both GCR isoforms in peripheral polymorphonuclear cells. Moreover, *GCR* expression and HPA axis function undergo a biphasic response during acute or subacute critical illness; this dissociation of reduced *GCR* expression and elevated cortisol might imply an abnormal stress response[42,43].

In coronavirus disease 2019 (COVID-19), results from the RECOVERY trial suggested significant benefits of steroid administration in critically-ill COVID-19 patients[44]. Specifically, the trial demonstrated that dexamethasone reduced mortality risk by 17%. A study in noncritically-ill COVID-19 patients showed that the HPA axis was activated. Patients exhibited an increase in cortisol, which was significantly higher than in those without COVID-19 infection, and these cortisol levels were associated with higher mortality rates[43]. Another study found that cortisol levels were lower in critically-ill COVID-19 patients compared to critically-ill non-COVID-19 patients[45]. In fact, nearly 70% of the COVID-19 critically-ill patients had plasma cortisol concentrations < 10 μg/dL, meeting CIRCI criteria. However, so far, data on COVID-19 and *GCR-a* expression are lacking.

Ascorbic acid (vitamin C) levels are depleted in critically-ill patients. This vitamin has been shown to play a crucial role in HPA axis function. The adrenal glands contain very high concentrations of ascorbic acid and use it to synthesize cortisol[46]. At the cellular level, vitamin C works synergistically with corticosteroids by restoring GCR function. Specifically, ascorbic acid reverses GCR oxidation, restoring GC-responsiveness in oxidant conditions. The end result is increased GC availability and GCR-α activation[47].

Overall, it seems that during critical illness *GCR* expression is independently regulated. This might explain the different responses seen in patients to exogenously administered steroids or endogenously secreted cortisol. Apart from *GCR* expression,

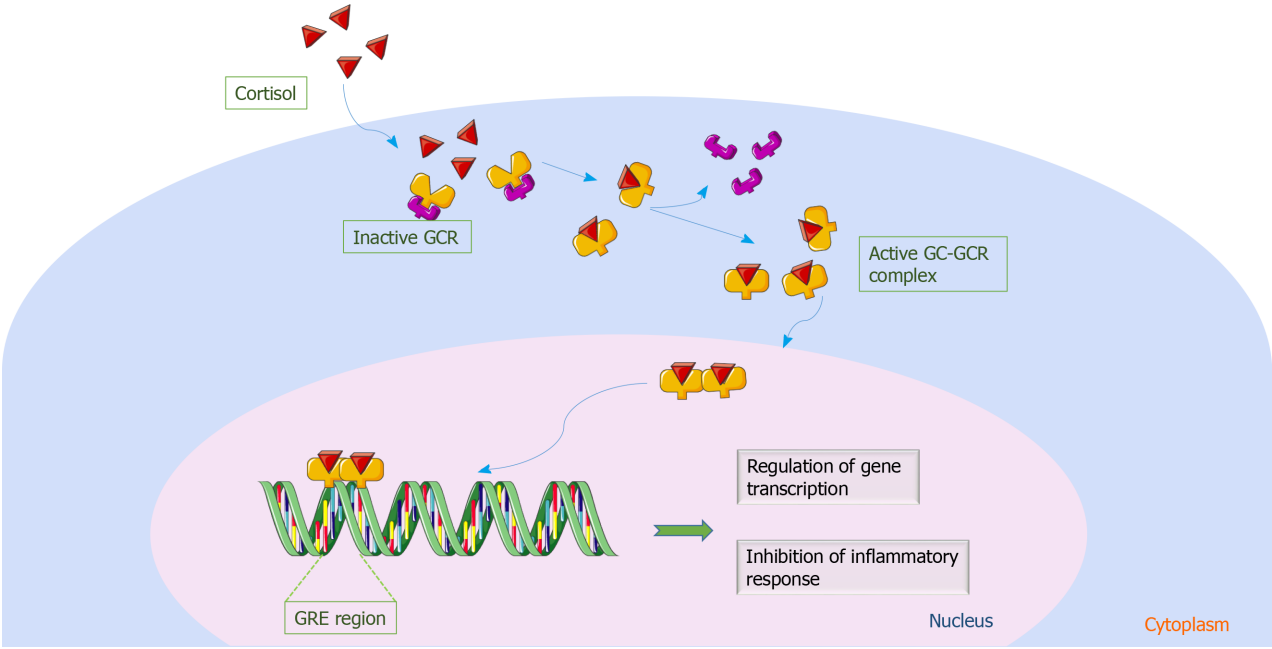

Figure 1 Cortisol signaling through the glucocorticoid receptor. Cortisol signaling is mediated by a ubiquitous intracellular receptor protein, the glucocorticoidreceptor (GCR). Once it binds to cortisol, the receptor-cortisol complex translocates from the cytosol to the nucleus. In the nucleus, the complex exerts transcriptional activation or repression by directly binding to genes that contain glucocorticoid (GC) responsive elements (GREs), resulting in the inhibition of the inflammatory response. GC-GCR: Cortisol-glucocorticoid receptor complex.

the role of post-translational modifications, GCR complex components and the efficiency of nuclear translocation of the GCR complex should be the focus of future clinical studies.

MR

The MR is, along with the GCR, a member of the steroid receptor superfamily of hormone-dependent transcription factors. The receptors are structurally and functionally related. Similar to GCR, MR is also localized in the cytosol and translocates into the nucleus after ligand binding. In the nucleus, the ligand-receptor complex recognizes specific DNA regions and activates target gene expression[48]. While GCR is relatively ubiquitously expressed and exclusively binds GCs, the MR shows a more restricted expression pattern, and can bind both aldosterone and cortisol. MR is mostly expressed in epithelial cells of renal distal tubules, colon, sweat and salivary glands, and is implicated in sodium reabsorption, water homeostasis and potassium secretion[49]. The classical ligand for MR is aldosterone, the main mineralocorticoid steroid hormone, through activation of the renin-angiotensin system. Aldosterone is the principal regulator of salt and water balance but can also act on nonepithelial sites, contributing significantly to cardiovascular disease[50].

Hyperreninemic hypoaldosteronism may occur during critical illness and has been associated with a greater proinflammatory status, a higher degree of acute organ failure, and worse prognosis. It has been attributed to impaired adrenal response to increasing renin levels[51-53]. The recent demonstration of the reduced mortality in septic shock patients treated with adjunctive GCs combined with fludrocortisone[9], and the effectiveness of angiotensin II in treating vasodilatory shock[54] has renewed interest in the role of the MR in critical illness[55].

The MR, originally thought to be expressed only in kidneys, is now known to have a wider distribution. At the organ level, it is expressed in heart, vessels, brain, and adipose tissue[56]. MR signaling induces inflammation, oxidative stress, and fibrosis/remodeling, thereby causing tissue and organ damage, particularly in the heart and vessels[49]. Furthermore, clinical studies have reported a beneficial outcome of MR antagonism in patients with cardiovascular diseases, mainly due to the prevention of inflammatory damage[57]. At the cellular level, MR is expressed in vascular cells, adipocytes, and immune cells[58]. This inflammatory involvement of MR and aldosterone in cardiovascular diseases suggests an association with immune

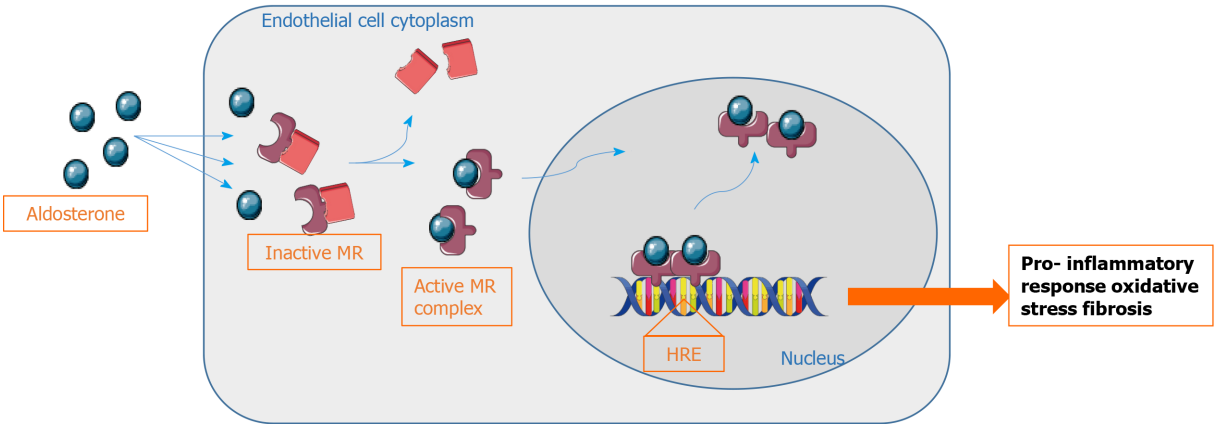

Figure 2 Mineralocorticoid signaling. The mineralocorticoid receptor is localized in the cytosol and translocates into the nucleus after ligand binding. In the nucleus, the aldosterone-mineralocorticoid receptor (MR) complex recognizes specific DNA regions, and activates target gene expression. MR signaling induces inflammation, oxidative stress, and fibrosis/remodeling, thereby causing tissue and organ damage. HRE: Hormone response element.

system changes. It has been consistently reported that aldosterone stimulation promotes proinflammatory responses[59,60]. In human leukocytes, MR expression has been shown in CD34+ hematopoietic progenitor cells, in peripheral blood T and B lymphocytes, macrophages, dendritic cells, and neutrophils[61]. In macrophages, lymphocytes and dendritic cells, MR signaling induces proinflammatory responses[62, 63]. The MR antagonist, spironolactone, was shown to have anti-inflammatory effects on cultured human peripheral blood mononuclear cells isolated from healthy subjects. Furthermore, angiotensin II induced aldosterone synthesis and enhanced cytokine production through an MR-dependent mechanism in human peripheral blood mononuclear cells[64,65]. In Figure 2, MR signaling is depicted.

11β-HSD

Both the innate and adaptive immune responses depend on the adhesion and migration of leukocytes across endothelial cells towards the inflamed site, where they protect against invading pathogens and repair damaged tissue. At the inflamed site, neutrophils undergo constitutive apoptosis to be removed from the inflammatory environment. Normally, acute inflammation rapidly resolves. However, failure to rapidly remove apoptotic neutrophils prolongs the inflammatory response. As mentioned above, endogenous GCs play a critical role in controlling inflammatory responses. Although GCs have an immunosuppressive effect on immune cells, they exert contradictory effects on neutrophils. At the inflamed sites they exert an anti-inflammatory effect by blunting neutrophil priming, whereas they increase circulating neutrophil count by delaying their apoptosis[66]. In circumstances of uncontrolled inflammation, polymorphonuclear cells can become detrimental by causing tissue injury and organ damage in critical illness[67].

Intracellular GC concentrations may vary compared to blood levels due to the action of the two 11β-HSD isozymes. 11β-HSD interconverts endogenous active cortisol and inert cortisone, which does not bind to GCR[68]. 11β-HSD2 (encoded by the *HSD11B2* gene) inactivates GCs, while 11β-HSD1 (encoded by *HSD11B1*) regenerates active GCs from inert keto forms, and hence modulates GC-regulated functions. Moreover, 11β-HSD1 is widely expressed in tissues that express high levels of GCR, suggesting that 11β-HSD1 modulates ligand access to GCR-α[68]. The degree of expression of these two isozymes may drastically affect local GC availability within individual cells and tissues.

11β-HSD1 is widely distributed, with its expression being highest in the liver, but is also expressed in adipose tissue, vessels, brain, and immune cells. In immune cells, 11β-HSD1 is primarily expressed in macrophages and lymphocytes, especially during inflammation[56,62,69]. 11β-HSD1 activates functionally inert GC precursors (cortisone) to active GCs (cortisol) within target tissues, and amplifies local GC actions. 11β-HSD2, except being expressed in the classical aldosterone-target tissues, is also expressed in the pancreas and the reproductive system[68]. 11β-HSD2 protects the MR from illicit occupancy by cortisol by inactivating cortisol within cells.

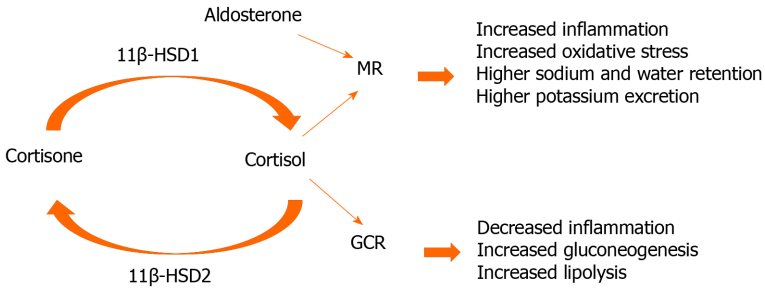

Figure 3 Glucocorticoid and mineralocorticoid receptor function, and the role of 11β-dehydrogenase isozymes. The ubiquitous glucocorticoid receptor (GCR) binds exclusively to cortisol, whereas the mineralocorticoid receptor (MR) is a receptor with equal affinity for mineralocorticoids and glucocorticoids. In epithelial tissues, MR activation leads to the expression of proteins regulating ionic and water transports, resulting in the reabsorption of sodium, and as a consequence an increase in extracellular volume, increase in blood pressure, and excretion of potassium to maintain a normal salt concentration in the body. The MR is activated by aldosterone and cortisol. Target cells for aldosterone express the enzyme 11β-dehydrogenase (11β-HSD) 2 that has no effect on aldosterone, but converts cortisol to cortisone, which has only a very weak affinity for the MR In essence, this enzyme "protects" the cell from cortisol and allows aldosterone to act appropriately. 11β-HSD1 activates functionally inert cortisone to active cortisol within target tissues and amplifies local glucocorticoid actions.

Aldosterone and cortisol bind the MR and have a similar affinity for the MR. The binding of cortisol or aldosterone to the MR results in different cellular responses[55]. Under physiological conditions, plasma cortisol levels are 100 × higher than aldosterone levels, and most MRs are occupied by GCs. The 11β-HSD enzymes regulate whether cortisol or aldosterone will bind to the MR. 11β-HSD type 2 metabolizes cortisol to inactive cortisone. Cortisone is unable to bind or activate the MR, and aldosterone occupies the MR. When 11β-HSD2 is not present or not functional, the ligand binding site on the MR is occupied by cortisol.

11β-HSD2 is mainly expressed in the classical aldosterone (mineralocorticoid)-target tissues, including the distal nephron, sweat and salivary glands, and colonic epithelium. 11β-HSD1 catalyzes the regeneration of active GCs, particularly in GC-target tissues, where it amplifies GC actions. *In vitro*, colocalization of the two enzymes within a cell results in their reciprocal regulation to minimize simultaneous expression [68]. Figure 3 diagrammatically shows the interplay between the corticoid receptors, their ligands and the 11β-HSD isozymes.

Although the immunosuppressive and anti-inflammatory activities of GCs are well documented, the expression of 11β-HSD enzymes in immune cells, and in particular polymorphonuclear cells, is not well understood. Overall, an anti-inflammatory role for 11β-HSD1 has been proposed in leukocytes, while studies have suggested that 11β-HSD2 is not expressed in these cells[70]. In human T-lymphoblastic leukemia cells, both 11β-HSD2 expression and reciprocal regulation of 11β-HSD1 and 11β-HSD2 have been shown to be associated with GC resistance[71,72].

Data for tissue resistance to GC activity are limited in critical illness. Indirect evidence suggesting altered tissue 11β-HSD activity comes from studies that found increased plasma cortisol:cortisone ratio in critically-ill septic and trauma patients[73, 74]. A recent study showed that in septic shock patients, sensitivity to GCs does not appear to be mediated by changes in the expression of the 11β-HSD2 isozyme[75]. Whether the reciprocal change in 11β-HSD1/11β-HSD2 is part of an adaptive response to inflammation or contributes to GC resistance remains to be established.

CONCLUSION

Studies on the expression of GCR, MR, 11β-HSD1 and 11β-HSD2 in critically-ill patients may allow a better understanding of homeostatic regulations of GCR and MR.

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REFERENCES

1 **Drucker D**, McLaughlin J. Adrenocortical dysfunction in acute medical illness. *Crit Care Med* 1986; **14**: 789-791 [PMID: 3017633 DOI: 10.1097/00003246-198609000-00006]

2 **Drucker D**, Shandling M. Variable adrenocortical function in acute medical illness. *Crit Care Med* 1985; **13**: 477-479 [PMID: 2986907 DOI: 10.1097/00003246-198506000-00007]

3 **Jurney TH**, Cockrell JL Jr, Lindberg JS, Lamiell JM, Wade CE. Spectrum of serum cortisol response to ACTH in ICU patients. Correlation with degree of illness and mortality. *Chest* 1987; **92**: 292-295 [PMID: 3038477 DOI: 10.1378/chest.92.2.292]

4 **Reincke M**, Allolio B, Würth G, Winkelmann W. The hypothalamic-pituitary-adrenal axis in critical illness: response to dexamethasone and corticotropin-releasing hormone. *J Clin Endocrinol Metab* 1993; **77**: 151-156 [PMID: 8392081 DOI: 10.1210/jcem.77.1.8392081]

5 **Dimopoulou I**, Stamoulis K, Ilias I, Tzanela M, Lyberopoulos P, Orfanos S, Armaganidis A, Theodorakopoulou M, Tsagarakis S. A prospective study on adrenal cortex responses and outcome prediction in acute critical illness: results from a large cohort of 203 mixed ICU patients. *Intensive Care Med* 2007; **33**: 2116-2121 [PMID: 17684725 DOI: 10.1007/s00134-007-0790-0]

6 **Vassiliadi DA**, Dimopoulou I, Tzanela M, Douka E, Livaditi O, Orfanos SE, Kotanidou A, Tsagarakis S. Longitudinal assessment of adrenal function in the early and prolonged phases of critical illness in septic patients: relations to cytokine levels and outcome. *J Clin Endocrinol Metab* 2014; **99**: 4471-4480 [PMID: 25148237 DOI: 10.1210/jc.2014-2619]

7 **Marik PE**, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M; American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; **36**: 1937-1949 [PMID: 18496365 DOI: 10.1097/CCM.0b013e31817603ba]

8 **Rhodes A**, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017; **43**: 304-377 [PMID: 28101605 DOI: 10.1007/s00134-017-4683-6]

9 **Annane D**, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit JF, Misset B, Ali Benali M, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, François B, Boulain T, Petitpas F, Constantin JM, Dhonneur G, Baudin F, Combes A, Bohé J, Loriferne JF, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E; CRICS-TRIGGERSEP Network. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med* 2018; **378**: 809-818 [PMID: 29490185 DOI: 10.1056/NEJMoa1705716]

10 **Annane D**, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaud P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; **288**: 862-871 [PMID: 12186604 DOI: 10.1001/jama.288.7.862]

11 **Sprung CL**, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; **358**: 111-124 [PMID: 18184957 DOI: 10.1056/NEJMoa071366]

12 **Venkatesh B**, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med* 2018; **378**: 797-808 [PMID: 29347874 DOI: 10.1056/NEJMoa1705835]

13 **Hollenberg SM**, Weinberger C, Ong ES, Cerelli G, Oro A, Lebo R, Thompson EB, Rosenfeld MG, Evans RM. Primary structure and expression of a functional human glucocorticoid receptor cDNA. *Nature* 1985; **318**: 635-641 [PMID: 2867473 DOI: 10.1038/318635a0]

14 **Kadmiel M**, Cidlowski JA. Glucocorticoid receptor signaling in health and disease. *Trends Pharmacol Sci* 2013; **34**: 518-530 [PMID: 23953592 DOI: 10.1016/j.tips.2013.07.003]

15 **Barnes PJ**, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med* 1997; **336**: 1066-1071 [PMID: 9091804 DOI: 10.1056/NEJM199704103361506]

16 **Göttlicher M**, Heck S, Herrlich P. Transcriptional cross-talk, the second mode of steroid hormone receptor action. *J Mol Med (Berl)* 1998; **76**: 480-489 [PMID: 9660166 DOI: 10.1007/s001090050242]

17 **Bamberger CM**, Bamberger AM, de Castro M, Chrousos GP. Glucocorticoid receptor beta, a potential endogenous inhibitor of glucocorticoid action in humans. *J Clin Invest* 1995; **95**: 2435-2441 [PMID: 7769088 DOI: 10.1172/JCI117943]

18 **Kino T**, Su YA, Chrousos GP. Human glucocorticoid receptor isoform beta: recent understanding of its potential implications in physiology and pathophysiology. *Cell Mol Life Sci* 2009; **66**: 3435-3448 [PMID: 19633971 DOI: 10.1007/s00018-009-0098-z]

19 **Oakley RH**, Sar M, Cidlowski JA. The human glucocorticoid receptor beta isoform. Expression, biochemical properties, and putative function. *J Biol Chem* 1996; **271**: 9550-9559 [PMID: 8621628 DOI: 10.1074/jbc.271.16.9550]

20 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]

21 **Chrousos GP**, Detera-Wadleigh SD, Karl M. Syndromes of glucocorticoid resistance. *Ann Intern Med* 1993; **119**: 1113-1124 [PMID: 8239231 DOI: 10.7326/0003-4819-119-11-199312010-00009]

22 **Marques AH**, Silverman MN, Sternberg EM. Glucocorticoid dysregulations and their clinical correlates. From receptors to therapeutics. *Ann N Y Acad Sci* 2009; **1179**: 1-18 [PMID: 19906229 DOI: 10.1111/j.1749-6632.2009.04987.x]

23 **Bamberger CM**, Schulte HM, Chrousos GP. Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. *Endocr Rev* 1996; **17**: 245-261 [PMID: 8771358 DOI: 10.1210/edrv-17-3-245]

24 **Colli LM**, do Amaral FC, Torres N, de Castro M. Interindividual glucocorticoid sensitivity in young healthy subjects: the role of glucocorticoid receptor alpha and beta isoforms ratio. *Horm Metab Res* 2007; **39**: 425-429 [PMID: 17578759 DOI: 10.1055/s-2007-980191]

25 **Koulouras VP**, Li R, Chen L, Hedenstierna GG. Effects of inhaled carbon monoxide and glucocorticoids in porcine endotoxin sepsis. *Int J Clin Exp Med* 2011; **4**: 53-66 [PMID: 21394286]

26 **Li F**, Xu RB. Changes in canine leukocyte glucocorticoid receptors during endotoxin shock. *Circ Shock* 1988; **26**: 99-105 [PMID: 3056634]

27 **Reichardt HM**, Umland T, Bauer A, Kretz O, Schütz G. Mice with an increased glucocorticoid receptor gene dosage show enhanced resistance to stress and endotoxic shock. *Mol Cell Biol* 2000; **20**: 9009-9017 [PMID: 11073999 DOI: 10.1128/mcb.20.23.9009-9017.2000]

28 **Stith RD**, McCallum RE. Down regulation of hepatic glucocorticoid receptors after endotoxin treatment. *Infect Immun* 1983; **40**: 613-621 [PMID: 6840856 DOI: 10.1128/IAI.40.2.613-621.1983]

29 **Da J**, Chen L, Hedenstierna G. Nitric oxide up-regulates the glucocorticoid receptor and blunts the inflammatory reaction in porcine endotoxin sepsis. *Crit Care Med* 2007; **35**: 26-32 [PMID: 17095945 DOI: 10.1097/01.CCM.0000250319.91575.BB]

30 **Abraham MN**, Jimenez DM, Fernandes TD, Deutschman CS. Cecal Ligation and Puncture Alters Glucocorticoid Receptor Expression. *Crit Care Med* 2018; **46**: e797-e804 [PMID: 29787416 DOI: 10.1097/CCM.0000000000003201]

31 **Bergquist M**, Nurkkala M, Rylander C, Kristiansson E, Hedenstierna G, Lindholm C. Expression of the glucocorticoid receptor is decreased in experimental Staphylococcus aureus sepsis. *J Infect* 2013; **67**: 574-583 [PMID: 23933016 DOI: 10.1016/j.jinf.2013.07.028]

32 **Goodwin JE**, Feng Y, Velazquez H, Sessa WC. Endothelial glucocorticoid receptor is required for protection against sepsis. *Proc Natl Acad Sci USA* 2013; **110**: 306-311 [PMID: 23248291 DOI: 10.1073/pnas.1210200110]

33 **Kamiyama K**, Matsuda N, Yamamoto S, Takano K, Takano Y, Yamazaki H, Kageyama S, Yokoo H, Nagata T, Hatakeyama N, Tsukada K, Hattori Y. Modulation of glucocorticoid receptor expression, inflammation, and cell apoptosis in septic guinea pig lungs using methylprednisolone. *Am J Physiol Lung Cell Mol Physiol* 2008; **295**: L998-L1006 [PMID: 18836031 DOI: 10.1152/ajplung.00459.2007]

34 **Ledderose C**, Möhnle P, Limbeck E, Schütz S, Weis F, Rink J, Briegel J, Kreth S. Corticosteroid resistance in sepsis is influenced by microRNA-124--induced downregulation of glucocorticoid receptor-α. *Crit Care Med* 2012; **40**: 2745-2753 [PMID: 22846781 DOI: 10.1097/CCM.0b013e31825b8ebc]

35 **Guerrero J**, Gatica HA, Rodríguez M, Estay R, Goecke IA. Septic serum induces glucocorticoid resistance and modifies the expression of glucocorticoid isoforms receptors: a prospective cohort study and *in vitro* experimental assay. *Crit Care* 2013; **17**: R107 [PMID: 23759144 DOI: 10.1186/cc12774]

36 **Molijn GJ**, Koper JW, van Uffelen CJ, de Jong FH, Brinkmann AO, Bruining HA, Lamberts SW. Temperature-induced down-regulation of the glucocorticoid receptor in peripheral blood mononuclear leucocyte in patients with sepsis or septic shock. *Clin Endocrinol (Oxf)* 1995; **43**: 197-203 [PMID: 7554315 DOI: 10.1111/j.1365-2265.1995.tb01915.x]

37 **Dekelbab BH**, Witchel SF, DeFranco DB. TNF-alpha and glucocorticoid receptor interaction in L6 muscle cells: a cooperative downregulation of myosin heavy chain. *Steroids* 2007; **72**: 705-712 [PMID: 17624386 DOI: 10.1016/j.steroids.2007.05.007]

38 **Bergquist M**, Lindholm C, Strinnholm M, Hedenstierna G, Rylander C. Impairment of neutrophilic glucocorticoid receptor function in patients treated with steroids for septic shock. *Intensive Care Med Exp* 2015; **3**: 59 [PMID: 26215823 DOI: 10.1186/s40635-015-0059-9]

39 **Sigal GA**, Maria DA, Katayama ML, Wajchenberg BL, Brentani MM. Glucocorticoid receptors in mononuclear cells of patients with sepsis. *Scand J Infect Dis* 1993; **25**: 245-248 [PMID: 8511519 DOI: 10.3109/00365549309008491]

40 **Vardas K**, Ilia S, Sertedaki A, Charmandari E, Briassouli E, Goukos D, Apostolou K, Psarra K,

Botoula E, Tsagarakis S, Magira E, Routsi C, Stratakis CA, Nanas S, Briassoulis G. Increased glucocorticoid receptor expression in sepsis is related to heat shock proteins, cytokines, and cortisol and is associated with increased mortality. *Intensive Care Med Exp* 2017; **5**: 10 [PMID: 28224564 DOI: 10.1186/s40635-017-0123-8]

41 **Siebig S**, Meinel A, Rogler G, Klebl E, Wrede CE, Gelbmann C, Froh S, Rockmann F, Bruennler T, Schoelmerich J, Langgartner J. Decreased cytosolic glucocorticoid receptor levels in critically ill patients. *Anaesth Intensive Care* 2010; **38**: 133-140 [PMID: 20191789 DOI: 10.1177/0310057X1003800122]

42 **Vassiliou AG**, Floros G, Jahaj E, Stamogiannos G, Gennimata S, Vassiliadi DA, Tsagarakis S, Tzanela M, Ilias I, Orfanos SE, Kotanidou A, Dimopoulou I. Decreased glucocorticoid receptor expression during critical illness. *Eur J Clin Invest* 2019; **49**: e13073 [PMID: 30703253 DOI: 10.1111/eci.13073]

43 **Vassiliou AG**, Stamogiannos G, Jahaj E, Botoula E, Floros G, Vassiliadi DA, Ilias I, Tsagarakis S, Tzanela M, Orfanos SE, Kotanidou A, Dimopoulou I. Longitudinal evaluation of glucocorticoid receptor alpha/beta expression and signalling, adrenocortical function and cytokines in critically ill steroid-free patients. *Mol Cell Endocrinol* 2020; **501**: 110656 [PMID: 31756425 DOI: 10.1016/j.mce.2019.110656]

44 **RECOVERY Collaborative Group**. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]

45 **Mao Y**, Xu B, Guan W, Xu D, Li F, Ren R, Zhu X, Gao Y, Jiang L. The Adrenal Cortex, an Underestimated Site of SARS-CoV-2 Infection. *Front Endocrinol (Lausanne)* 2020; **11**: 593179 [PMID: 33488517 DOI: 10.3389/fendo.2020.593179]

46 **Patak P**, Willenberg HS, Bornstein SR. Vitamin C is an important cofactor for both adrenal cortex and adrenal medulla. *Endocr Res* 2004; **30**: 871-875 [PMID: 15666839 DOI: 10.1081/erc-200044126]

47 **Meduri GU**. New rationale for glucocorticoid treatment in septic shock. *J Chemother* 1999; **11**: 541-550 [PMID: 10678798 DOI: 10.1179/joc.1999.11.6.541]

48 **Funder JW**. Glucocorticoid and mineralocorticoid receptors: biology and clinical relevance. *Annu Rev Med* 1997; **48**: 231-240 [PMID: 9046958 DOI: 10.1146/annurev.med.48.1.231]

49 **Gomez-Sanchez E**, Gomez-Sanchez CE. The multifaceted mineralocorticoid receptor. *Compr Physiol* 2014; **4**: 965-994 [PMID: 24944027 DOI: 10.1002/cphy.c130044]

50 **Funder JW**. Aldosterone and Mineralocorticoid Receptors-Physiology and Pathophysiology. *Int J Mol Sci* 2017; **18** [PMID: 28492512 DOI: 10.3390/ijms18051032]

51 **du Cheyron D**, Bouchet B, Cauquelin B, Guillotin D, Ramakers M, Daubin C, Ballet JJ, Charbonneau P. Hyperreninemic hypoaldosteronism syndrome, plasma concentrations of interleukin-6 and outcome in critically ill patients with liver cirrhosis. *Intensive Care Med* 2008; **34**: 116-124 [PMID: 17906854 DOI: 10.1007/s00134-007-0864-z]

52 **du Cheyron D**, Lesage A, Daubin C, Ramakers M, Charbonneau P. Hyperreninemic hypoaldosteronism: a possible etiological factor of septic shock-induced acute renal failure. *Intensive Care Med* 2003; **29**: 1703-1709 [PMID: 14551679 DOI: 10.1007/s00134-003-1986-6]

53 **Muto S**, Fujisawa G, Natsume T, Asano Y, Yaginuma T, Hosoda S, Saito T. Hyponatremia and hyperreninemic hypoaldosteronism in a critically ill patient: combination of insensitivity to angiotensin II and tubular unresponsiveness to mineralocorticoid. *Clin Nephrol* 1990; **34**: 208-213 [PMID: 2176579]

54 **Khanna A**, Ostermann M, Bellomo R. Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med* 2017; **377**: 2604 [PMID: 29281568 DOI: 10.1056/NEJMc1714511]

55 **Nethathe GD**, Cohen J, Lipman J, Anderson R, Feldman C. Mineralocorticoid Dysfunction during Critical Illness: A Review of the Evidence. *Anesthesiology* 2020; **133**: 439-457 [PMID: 32501957 DOI: 10.1097/ALN.0000000000003365]

56 **Cole TJ**, Young MJ. 30 YEARS OF THE MINERALOCORTICOID RECEPTOR: Mineralocorticoid receptor null mice: informing cell-type-specific roles. *J Endocrinol* 2017; **234**: T83-T92 [PMID: 28550025 DOI: 10.1530/JOE-17-0155]

57 **Rossignol P**, Ménard J, Fay R, Gustafsson F, Pitt B, Zannad F. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy. *J Am Coll Cardiol* 2011; **58**: 1958-1966 [PMID: 22032706 DOI: 10.1016/j.jacc.2011.04.049]

58 **Gilbert KC**, Brown NJ. Aldosterone and inflammation. *Curr Opin Endocrinol Diabetes Obes* 2010; **17**: 199-204 [PMID: 20422780 DOI: 10.1097/med.0b013e3283391989]

59 **Herrada AA**, Campino C, Amador CA, Michea LF, Fardella CE, Kalergis AM. Aldosterone as a modulator of immunity: implications in the organ damage. *J Hypertens* 2011; **29**: 1684-1692 [PMID: 21826023 DOI: 10.1097/HJH.0b013e32834a4c75]

60 **Muñoz-Durango N**, Barake MF, Letelier NA, Campino C, Fardella CE, Kalergis AM. Immune system alterations by aldosterone during hypertension: from clinical observations to genomic and non-genomic mechanisms leading to vascular damage. *Curr Mol Med* 2013; **13**: 1035-1046 [PMID: 23590758 DOI: 10.2174/1566524011313060015]

61 **Grafte-Faure S**, Leveque C, Vasse M, Soria C, Norris V, Vannier JP. Effects of glucocorticoids and

mineralocorticoids on proliferation and maturation of human peripheral blood stem cells. *Am J Hematol* 1999; **62**: 65-73 [PMID: 10508999 DOI: 10.1002/(sici)1096-8652(199910)62:2<65::aid-ajh1>3.0.co;2-g]

62 **Bene NC**, Alcaide P, Wortis HH, Jaffe IZ. Mineralocorticoid receptors in immune cells: emerging role in cardiovascular disease. *Steroids* 2014; **91**: 38-45 [PMID: 24769248 DOI: 10.1016/j.steroids.2014.04.005]

63 **van der Heijden CDCC**, Deinum J, Joosten LAB, Netea MG, Riksen NP. The mineralocorticoid receptor as a modulator of innate immunity and atherosclerosis. *Cardiovasc Res* 2018; **114**: 944-953 [PMID: 29668907 DOI: 10.1093/cvr/cvy092]

64 **Miura R**, Nakamura K, Miura D, Miura A, Hisamatsu K, Kajiya M, Hashimoto K, Nagase S, Morita H, Fukushima Kusano K, Emori T, Ishihara K, Ohe T. Aldosterone synthesis and cytokine production in human peripheral blood mononuclear cells. *J Pharmacol Sci* 2006; **102**: 288-295 [PMID: 17072102 DOI: 10.1254/jphs.fp0060801]

65 **Miura R**, Nakamura K, Miura D, Miura A, Hisamatsu K, Kajiya M, Nagase S, Morita H, Fukushima Kusano K, Ohe T, Ishihara K. Anti-inflammatory effect of spironolactone on human peripheral blood mononuclear cells. *J Pharmacol Sci* 2006; **101**: 256-259 [PMID: 16837769 DOI: 10.1254/jphs.sc0060049]

66 **Ronchetti S**, Ricci E, Migliorati G, Gentili M, Riccardi C. How Glucocorticoids Affect the Neutrophil Life. *Int J Mol Sci* 2018; **19** [PMID: 30563002 DOI: 10.3390/ijms19124090]

67 **McDonald B**. Neutrophils in critical illness. *Cell Tissue Res* 2018; **371**: 607-615 [PMID: 29247324 DOI: 10.1007/s00441-017-2752-3]

68 **Chapman KE**, Coutinho AE, Zhang Z, Kipari T, Savill JS, Seckl JR. Changing glucocorticoid action: 11β-hydroxysteroid dehydrogenase type 1 in acute and chronic inflammation. *J Steroid Biochem Mol Biol* 2013; **137**: 82-92 [PMID: 23435016 DOI: 10.1016/j.jsbmb.2013.02.002]

69 **Zhang Z**, Coutinho AE, Man TY, Kipari TMJ, Hadoke PWF, Salter DM, Seckl JR, Chapman KE. Macrophage 11β-HSD-1 deficiency promotes inflammatory angiogenesis. *J Endocrinol* 2017; **234**: 291-299 [PMID: 28676523 DOI: 10.1530/JOE-17-0223]

70 **Gilmour JS**, Coutinho AE, Cailhier JF, Man TY, Clay M, Thomas G, Harris HJ, Mullins JJ, Seckl JR, Savill JS, Chapman KE. Local amplification of glucocorticoids by 11 beta-hydroxysteroid dehydrogenase type 1 promotes macrophage phagocytosis of apoptotic leukocytes. *J Immunol* 2006; **176**: 7605-7611 [PMID: 16751407 DOI: 10.4049/jimmunol.176.12.7605]

71 **Agnew EJ**, Ivy JR, Stock SJ, Chapman KE. Glucocorticoids, antenatal corticosteroid therapy and fetal heart maturation. *J Mol Endocrinol* 2018; **61**: R61-R73 [PMID: 29720513 DOI: 10.1530/JME-18-0077]

72 **Sai S**, Nakagawa Y, Yamaguchi R, Suzuki M, Sakaguchi K, Okada S, Seckl JR, Ohzeki T, Chapman KE. Expression of 11beta-hydroxysteroid dehydrogenase 2 contributes to glucocorticoid resistance in lymphoblastic leukemia cells. *Leuk Res* 2011; **35**: 1644-1648 [PMID: 21794917 DOI: 10.1016/j.leukres.2011.07.002]

73 **Cohen J**, Smith ML, Deans RV, Pretorius CJ, Ungerer JP, Tan T, Jones M, Venkatesh B. Serial changes in plasma total cortisol, plasma free cortisol, and tissue cortisol activity in patients with septic shock: an observational study. *Shock* 2012; **37**: 28-33 [PMID: 21993448 DOI: 10.1097/SHK.0b013e318239b809]

74 **Venkatesh B**, Cohen J, Hickman I, Nisbet J, Thomas P, Ward G, Hall J, Prins J. Evidence of altered cortisol metabolism in critically ill patients: a prospective study. *Intensive Care Med* 2007; **33**: 1746-1753 [PMID: 17558491 DOI: 10.1007/s00134-007-0727-7]

75 **Cohen J**, Pretorius CJ, Ungerer JP, Cardinal J, Blumenthal A, Presneill J, Gatica-Andrades M, Jarrett P, Lassig-Smith M, Stuart J, Dunlop R, Starr T, Venkatesh B. Glucocorticoid Sensitivity Is Highly Variable in Critically Ill Patients With Septic Shock and Is Associated With Disease Severity. *Crit Care Med* 2016; **44**: 1034-1041 [PMID: 26963327 DOI: 10.1097/CCM.0000000000001633]

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MINIREVIEWS

Predictive modeling in neurocritical care using causal artificial intelligence

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Abstract

Artificial intelligence (AI) and digital twin models of various systems have long been used in industry to test products quickly and efficiently. Use of digital twins in clinical medicine caught attention with the development of Archimedes, an AI model of diabetes, in 2003. More recently, AI models have been applied to the fields of cardiology, endocrinology, and undergraduate medical education. The use of digital twins and AI thus far has focused mainly on chronic disease management, their application in the field of critical care medicine remains much less explored. In neurocritical care, current AI technology focuses on interpreting electroencephalography, monitoring intracranial pressure, and prognosticating outcomes. AI models have been developed to interpret electroencephalograms by helping to annotate the tracings, detecting seizures, and identifying brain activation in unresponsive patients. In this mini-review we describe the challenges and opportunities in building an actionable AI model pertinent to neurocritical care that can be used to educate the newer generation of clinicians and augment clinical decision making.

Key Words: Artificial intelligence; Digital twin; Critical care; Neurology; Causal artificial

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Core Tip: The modern clinical environment is increasingly surrounded by data. The existing literature is sparse concerning the creation of a "digital twin" artificial intelligence (AI) model as a tool for education and potentially clinical decision making in the neurologic intensive care unit setting. This mini review will give readers an introduction to applications of AI inside and outside of healthcare, the idea of the "digital twin" as a model of disease, how AI has been applied in neurocritical care, and methodology for building a neurocritical care digital twin AI model that is based on a solid understanding of underlying pathophysiology.

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INTRODUCTION

The National Academy of Medicine released a report in 2010 highlighting recommendations with regards to what the United States Department of Health and Human Services can do to improve population health[1]. One of the suggested approaches in the report highlighted that the biological and environmental causes of poor health are complex and inter-related. Computer simulation models and other novel analytical tools such as artificial intelligence (AI) can potentially elucidate these relationships and help us better understand the underlying pathophysiology. The main pre-requisite for such models is that they should be built on the foundation of plausible biological and physiological understanding and algorithms.

In a world increasingly surrounded by data, digital twins have been used in everything from wind turbines to cities to spacecraft to model processes and preempt problems[2]. The European Union has even been attempting to create a digital twin model of planet earth to better forecast weather and predict climate change[3]. It would not be unreasonable to think that these technological advances could be applied to the field of healthcare as well. With the recent rise of electronic medical records, more sophisticated monitoring, and molecular biology in healthcare, digital twin technology provides a unique opportunity to personalize medicine to the level of the individual patient[4]. Digital twins are able to integrate vast amounts of data to create digital replicas of the physical environment and acts as models that are able to inform clinical decision making in an actionable way[5].

There is a need to evaluate the status of research on the use of simulation applications by various medical and surgical specialties to identify and recommend areas of research wherein there is a significant knowledge gap. This urgency is further compounded by the issue that medical errors are one of the leading causes of death in the United States[6]. Whether the use of simulation models by expert clinicians (or trainees) will improve the overall patient outcomes in clinical practice remains a challenging research question. Yet, it would be unquestionably helpful to test medical decisions in an "in silico" environment before attempting our treatment strategies on real patients. Such a testing environment would be especially useful to evaluate management decisions of uncertain benefit the patients.

WHAT IS A DIGITAL TWIN?

Digital twins are a concept from engineering whereby digital models of a system are built to allow testing of products more efficiently and economically[2]. The development of the use of a "Twin AI" for predictive modeling in health care first caught attention in 2003 with the Archimedes project, which sought to model the

complicated management of diabetes and was validated to 18 different trials involving diabetes with a very high correlation despite the fact that the trial data was not used to develop the model[7]. These new digital twin AI models are able to integrate the various demographic and individual-specific factors that complicate diabetes management on a level that the human brain cannot[8]. In addition to proving an accurate predictive model at the population level, Archimedes has also been shown to make accurate predictions for individuals[9]. The high accuracy of prediction and fidelity of the model led to its use in in-silico clinical trials, thereby saving crucial time, millions of dollars and most importantly shielding patients from being exposed to harm from interventions that may or may not have been beneficial[8,10].

In clinical practice, the concept of digital twins has also been applied to the fields of cardiology and endocrinology[11-13]. In cardiology, a few digital twin models have recently been developed to allow clinicians to provide precise care tailored to the patient by considering inter-individual variability and integrating the wide spectrum of biologic, environmental, and lifestyle data that influence cardiovascular outcomes. However, there is still much work to be done before these models become common in clinical practice[12]. Additionally, AI has been used to create large-scale synthetic data for training of other machine learning algorithms[14]. In Endocrinology, an AI model of the pancreas has been developed for use in the critical care setting to manage patients' glucose levels[13].

In the field of undergraduate medical education, programs that utilize an AI model of physiology, such as justphysiology and sycamore, have recently been incorporated in curricula[15]. These simulations afford the benefits of providing a safe practice environment for trainees, exposing students to a range of pathology that is not restricted to the available patient population, and getting students to engage actively with the underlying physiological principles involved in chronic disease management. While these models are based on solid mathematical models of human physiology, they are focused on chronic disease management rather than the acute pathology seen in critical care units and are unable to adapt to prospective data from real-time patients.

Digital twin AI models can be developed as "associative models" (mostly data driven) or "actionable models" (based on causal inference). Associative models are built using retrospective electronic health record data, which is more readily available. Utilizing a database of 703782 patients, Tomašev *et al*[16] created an associative AI model that was able to predict 55.8% of inpatient acute kidney injury events at 48 h. While these models are great at providing prognostic information, they do not offer information on the effects of different interventions on patient care. Additionally, these models are purely data-driven and do not consider the underlying physiology or causal pathways of disease in their development. The clinical utility of these models is limited by the lack of precision and underperformance in the clinical setting. In comparison, actionable AI models (or, as we have previously coined them, "Causal AI" models) are developed with explicit consideration of causal pathways, providing greater clinical utility in predicting the outcome of a given intervention as well as providing clinicians a better understanding of how the AI model is reaching its conclusions[17,18].

AI APPLICATIONS IN NEUROCRITICAL CARE

While digital twin models have been developed and tested for use in the fields of diabetes, cardiology, and sepsis management, this model has not yet been tested in the neurocritical care (NCC) unit. Yet, the NCC unit is an optimal place to develop "Twin AI" model. Within the NCC unit, there is a large need to integrate vast amounts of data including intracranial pressure, electroencephalography, hemodynamics, ventilation parameters, body temperature, and fluid balance, along with the neurological exam to allow neurointensivists to make time-sensitive and impactful decisions for patient care[19,20]. Use of AI to augment clinical decision making also has the potential to reduce costs and improve access to quality care for patients in areas where the expertise of a NCC physician is not readily available[21].

In NCC, current AI technology focuses on interpreting electroencephalography, monitoring intracranial pressure (ICP), and prognosticating outcomes[22]. AI models have been developed to interpret electroencephalograms by helping to annotate the tracings, detecting seizures, and identifying brain activation in unresponsive patients [23-26]. More specific models have been developed to analyze waveforms of ICP to detect artifact in ICP measurements, predict future ICP levels, determine which

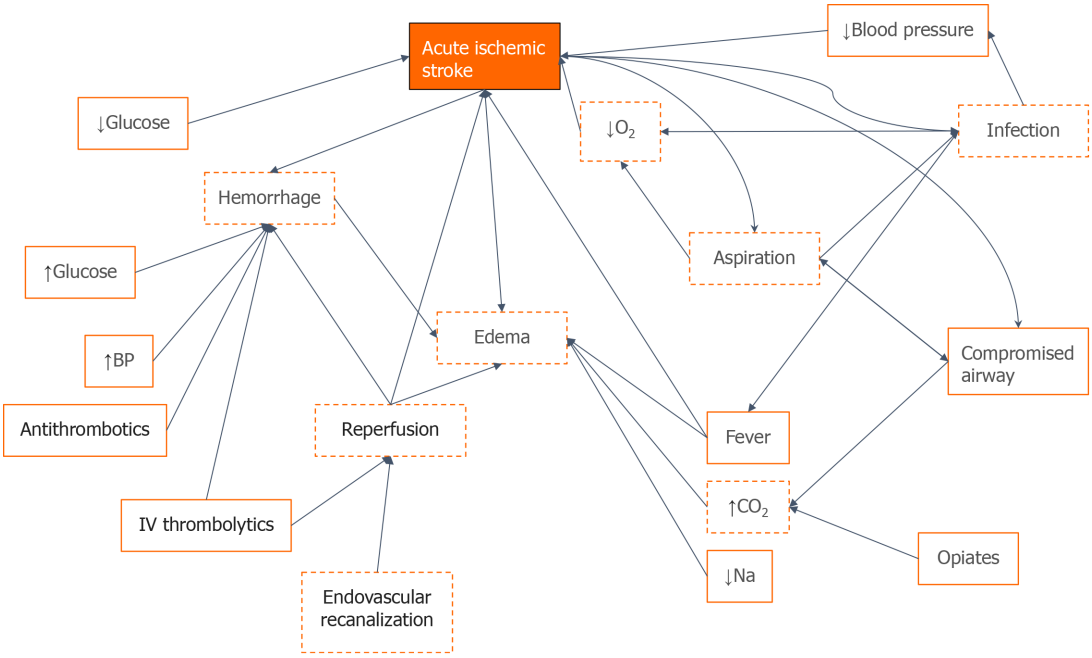

Figure 1 A directed acyclic graph for stroke patients that link concepts through Bayesian networks built from an underlying understanding of disease processes. Orange boxes represent concepts, orange solid lines represent actionable factors, dashed red lines represent semi-actionable factors, arrows represent Bayesian connections between different variables. O_2: Oxygen; CO_2; Carbon dioxide; BP: Blood pressure; Na: Sodium.

patients are at risk of increased ICP, and prognosticate mortality[27-30]. AI models are able to provide prognostic information for patients with subarachnoid hemorrhage, traumatic brain injury, or who are at risk for health-care associated ventriculitis and meningitis[31-33]. In the European Union, technologies such as Avert-IT have been developed for use in the critical unit to predict hypotensive events in patients with traumatic brain injury[34]. Still, to our knowledge, a model that integrates all the measures available in the NCC unit to create a broad digital twin model of the patient does not yet exist.

Having a digital twin model that can accurately replicate patient physiology in the NCC environment would have distinct advantages. Such a model would allow training physicians to sharpen their clinical decision making and provide opportunities to trial different treatments without ever risking patient safety. Preliminary results of a digital twin model used to predict response to treatments in patients in the intensive care unit with sepsis within the first 24 h have shown that creating such a model is possible[18].

A similar approach should be feasible for neurocritical diseases and illustrations of how these models could be conceptually built for application in NCC are shown in Figures 1 and 2. In applying this model to a patient with ischemic stroke, for example, factors such as blood pressure, glucose levels, securing an airway, and giving anticoagulation, thrombolytics, or opiate medication are all actionable factors that can be input into the AI model. These actions will affect certain semi-actionable factors and the overarching concept in the digital twin AI model such as hemorrhage, edema, aspiration, and, ultimately, ischemic stroke, all connected by Bayesian networks. Similar models such as this will be built for other disease states within the NCC unit as well. With this digital twin of the patient, trainees will be able to test different interventions and get real-time feedback on the effects of their intervention without ever having to worry about potential harm to the actual patient.

UTILITY IN MEDICAL EDUCATION

The central purpose of medical education, learning and assessment is to optimize patient care, avoid harm to the patients, and improve the cognitive skills of practitioners and learners alike. Continual learning and retooling are a vital aspect of practicing medicine. A major concern in healthcare and medical education is that initial training must be provided with minimal risk to patients. Moreover, maintenance of skills among busy physicians practicing in the community is an ever-

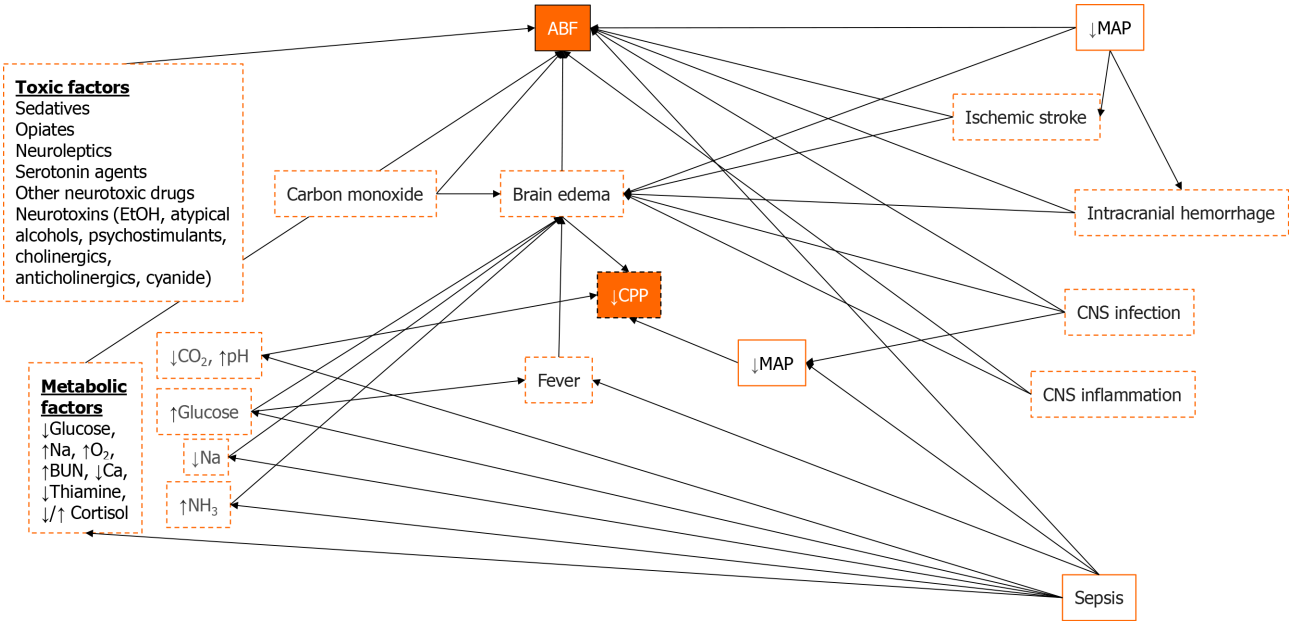

Figure 2 A directed acyclic graph for acute brain failure that links concepts through Bayesian networks built from an underlying understanding of disease processes. Orange boxes represent concepts, orange solid lines represent actionable factors, dashed red lines represent semi-actionable factors, arrows represent Bayesian connections between different variables. MAP: Mean arterial pressure; CPP: Cerebral perfusion pressure; NH_3: Ammonium; Na: Sodium; BUN: Blood urea nitrogen; Ca: Calcium; O_2: Oxygen; ABF: Acute brain failure; CNS: Central nervous system.

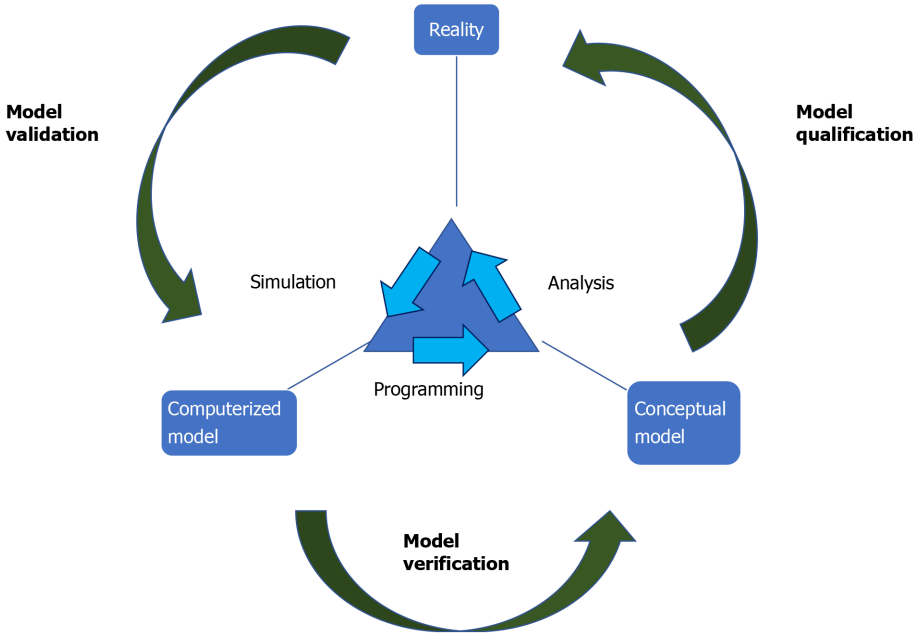

Figure 3 Accurate verification and validation of the model using the iterative steps of programming, simulation, and analysis[39].

growing concern.

The utilization of a virtual environment to enhance the procedural performance through simulation is not a new concept. High-fidelity simulators are now a prerequisite for gaining proficiency in endoscopic, laparoscopic, and robotic surgery [35]. With the advent of minimally invasive surgical procedures, it became evident that there is a dire need for skill acquisition outside the operating theater before attempting a similar procedure on real patients[36]. Despite the compelling evidence in various areas of clinical medicine, the world of critical care medicine has lagged in providing a well-equipped platform for cognitive training and skill acquisition in the virtual environment.

Creating an "in-silico" model or a "digital twin" allows learning, cognitive skill acquisition and refinement in an environment that does not expose patients to the risk of uncertain interventions and offers the ability to test the cognitive domains of decision making in real time with rapid assessment and perceptible metrics. We envision creating such an educational tool with potential refinement to a level that it can be used as a digital twin to assess the effect of an intervention in the virtual environment without exposing actual patients to risk. Early in the medical education program, even low fidelity patient presentations can be a good fit for assessment purposes if appropriately matched for the level of learner and educational level. The digital twin AI model can not only be used for medical education but can also be utilized for summative assessment where the cognitive competency of the critical care trainees can be assessed in an objective manner to determine if he/she can be graduated to the next level.

BUILDING THE AI MODEL–CHALLENGES AND ETHICAL CONSIDERATIONS

AI model should be constructed in such a way that they augment, rather than attempt to replace, the clinician's judgment[37]. Transparent AI models based on our understanding of pathophysiology are more likely to be trusted, and consequently implemented into practice, by clinicians than "black-box" AI models that reach their conclusions through multiple layers of neural networks. Actionable AI models should therefore be based on sound biology and should aim to replicate real-life disease processes.

Building these models starts with directed acyclic graphs (DAGs). DAGs are diagrams that connect concepts (defined as variables) through Bayesian networks that represent the probabilistic relationship between those concepts (Figures 1 and 2). These DAGs, built from an understanding of underlying pathophysiology and in collaboration with content experts act as a base for the development of the AI model. Expert knowledge is necessary to develop the rules that will connect the variables (*i.e.*, what would be expected to happen to the connected variables after a certain change in one of them). To avoid bias, we intend to gain expert consensus on our rules using DELPHI method, an iterative process of surveying experts that seeks to integrate knowledge about a specific field, before constructing the AI models. These DAGs are then converted into statements that can then be transformed into code and incorporated into the AI model. Once the model is developed, it will be prospectively validated by comparing its predictions to the actual clinical findings in real patients, the irreplaceable gold standard for any AI application to health care. This process will go through multiple cycle or iterations of computer modeling (programming), comparing the performance of the digital twin in an "in-silico" environment (simulation) and gathering of qualitative and quantitative data to improve the performance of the model (analysis) (Figure 3). This process was piloted in our feasibility study for the digital twin of critically ill sepsis patients[18].

While a digital twin model in healthcare could lead to a more accurate, individualized model of health and diseased states, this new technology also brings with it ethical questions, such as who will have access to this new technology, how this technology may lead to a deemphasizing of patient autonomy in favor of algorithms, and how compiling large amounts of health data may lead to identification of trends that may justify future divisiveness and segregation[38]. In creating any new AI technology, we must be cognizant of the ethical and safety implications of the new technology and ensure that any new AI model acts to augment rather than supersede clinician judgement. Like any nascent technology, AI models can be initially erroneous or insufficiently accurate; validation is therefore essential for their refinement and must always be conducted before their implementation.

CONCLUSION

While digital twin models have been established in the fields of cardiology, endocrinology, and undergraduate medical education, a validated model has not yet been adopted to training and clinical practice in the field of NCC. We propose to develop actionable digital twin models based on an understanding of the underlying pathophysiology of disease to train future physicians and potentially inform clinical

decision making in the complex environment of NCC.

REFERENCES

1 **Medicine Io**. For the Public's Health: The Role of Measurement in Action and Accountability. Washington, DC: The National Academies Press, 2011: 204 [PMID: 24983050 DOI: 10.17226/13005]
2 **Tao F**, Qi Q. Make more digital twins. *Nature* 2019; **573**: 490-491 [PMID: 31554984 DOI: 10.1038/d41586-019-02849-1]
3 **Voosen P**. Europe builds 'digital twin' of Earth to hone climate forecasts. *Science* 2020; **370**: 16-17 [PMID: 33004491 DOI: 10.1126/science.370.6512.16]
4 **Björnsson B**, Borrebaeck C, Elander N, Gasslander T, Gawel DR, Gustafsson M, Jörnsten R, Lee EJ, Li X, Lilja S, Martínez-Enguita D, Matussek A, Sandström P, Schäfer S, Stenmarker M, Sun XF, Sysoev O, Zhang H, Benson M; Swedish Digital Twin Consortium. Digital twins to personalize medicine. *Genome Med* 2019; **12**: 4 [PMID: 31892363 DOI: 10.1186/s13073-019-0701-3]
5 **Croatti A**, Gabellini M, Montagna S, Ricci A. On the Integration of Agents and Digital Twins in Healthcare. *J Med Syst* 2020; **44**: 161 [PMID: 32748066 DOI: 10.1007/s10916-020-01623-5]
6 **Makary MA**, Daniel M. Medical error-the third leading cause of death in the US. *BMJ* 2016; **353**: i2139 [PMID: 27143499 DOI: 10.1136/bmj.i2139]
7 **Eddy DM**, Schlessinger L. Validation of the archimedes diabetes model. *Diabetes Care* 2003; **26**: 3102-3110 [PMID: 14578246 DOI: 10.2337/diacare.26.11.3102]
8 **Kahn R**. Dealing with complexity in clinical diabetes: the value of archimedes. *Diabetes Care* 2003; **26**: 3168-3171 [PMID: 14578256 DOI: 10.2337/diacare.26.11.3168]
9 **Stern M**, Williams K, Eddy D, Kahn R. Validation of prediction of diabetes by the Archimedes model and comparison with other predicting models. *Diabetes Care* 2008; **31**: 1670-1671 [PMID: 18509203 DOI: 10.2337/dc08-0521]
10 **Eddy DM**, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. *Ann Intern Med* 2005; **143**: 251-264 [PMID: 16103469 DOI: 10.7326/0003-4819-143-4-200508160-00006]
11 **Chakshu NK**, Sazonov I, Nithiarasu P. Towards enabling a cardiovascular digital twin for human systemic circulation using inverse analysis. *Biomech Model Mechanobiol* 2021; **20**: 449-465 [PMID: 33064221 DOI: 10.1007/s10237-020-01393-6]
12 **Corral-Acero J**, Margara F, Marciniak M, Rodero C, Loncaric F, Feng Y, Gilbert A, Fernandes JF, Bukhari HA, Wajdan A, Martinez MV, Santos MS, Shamohammdi M, Luo H, Westphal P, Leeson P, DiAchille P, Gurev V, Mayr M, Geris L, Pathmanathan P, Morrison T, Cornelussen R, Prinzen F, Delhaas T, Doltra A, Sitges M, Vigmond EJ, Zacur E, Grau V, Rodriguez B, Remme EW, Niederer S, Mortier P, McLeod K, Potse M, Pueyo E, Bueno-Orovio A, Lamata P. The 'Digital Twin' to enable the vision of precision cardiology. *Eur Heart J* 2020; **41**: 4556-4564 [PMID: 32128588 DOI: 10.1093/eurheartj/ehaa159]
13 **DeJournett L**, DeJournett J. In Silico Testing of an Artificial-Intelligence-Based Artificial Pancreas Designed for Use in the Intensive Care Unit Setting. *J Diabetes Sci Technol* 2016; **10**: 1360-1371 [PMID: 27301982 DOI: 10.1177/1932296816653967]
14 **Mazumder O**, Roy D, Bhattacharya S, Sinha A, Pal A. Synthetic PPG generation from haemodynamic model with baroreflex autoregulation: a Digital twin of cardiovascular system. *Annu Int Conf IEEE Eng Med Biol Soc* 2019; **2019**: 5024-5029 [PMID: 31946988 DOI: 10.1109/EMBC.2019.8856691]
15 **Hester RL**, Pruett W, Clemmer J, Ruckdeschel A. Simulation of integrative physiology for medical education. *Morphologie* 2019; **103**: 187-193 [PMID: 31563456 DOI: 10.1016/j.morpho.2019.09.004]
16 **Tomašev N**, Glorot X, Rae JW, Zielinski M, Askham H, Saraiva A, Mottram A, Meyer C, Ravuri S, Protsyuk I, Connell A, Hughes CO, Karthikesalingam A, Cornebise J, Montgomery H, Rees G, Laing C, Baker CR, Peterson K, Reeves R, Hassabis D, King D, Suleyman M, Back T, Nielson C, Ledsam JR, Mohamed S. A clinically applicable approach to continuous prediction of future acute kidney injury. *Nature* 2019; **572**: 116-119 [PMID: 31367026 DOI: 10.1038/s41586-019-1390-1]
17 **Lal A**, Pinevich Y, Gajic O, Herasevich V, Pickering B. Artificial intelligence and computer simulation models in critical illness. *World J Crit Care Med* 2020; **9**: 13-19 [PMID: 32577412 DOI: 10.5492/wjccm.v9.i2.13]
18 **Lal A**, Li G, Cubro E, Chalmers S, Li H, Herasevich V, Dong Y, Pickering BW, Kilickaya O, Gajic O. Development and Verification of a Digital Twin Patient Model to Predict Specific Treatment Response During the First 24 Hours of Sepsis. *Crit Care Explor* 2020; **2**: e0249 [PMID: 33225302 DOI: 10.1097/CCE.0000000000000249]
19 **Al-Mufti F**, Kim M, Dodson V, Sursal T, Bowers C, Cole C, Scurlock C, Becker C, Gandhi C, Mayer SA. Machine Learning and Artificial Intelligence in Neurocritical Care: a Specialty-Wide Disruptive Transformation or a Strategy for Success. *Curr Neurol Neurosci Rep* 2019; **19**: 89 [PMID: 31720867 DOI: 10.1007/s11910-019-0998-8]
20 **Wartenberg KE**, Schmidt JM, Mayer SA. Multimodality monitoring in neurocritical care. *Crit Care Clin* 2007; **23**: 507-538 [PMID: 17900483 DOI: 10.1016/j.ccc.2007.06.002]
21 **Al-Mufti F**, Dodson V, Lee J, Wajswol E, Gandhi C, Scurlock C, Cole C, Lee K, Mayer SA.

Artificial intelligence in neurocritical care. *J Neurol Sci* 2019; **404**: 1-4 [PMID: 31302258 DOI: 10.1016/j.jns.2019.06.024]

22 **Chaudhry F**, Hunt RJ, Hariharan P, Anand SK, Sanjay S, Kjoller EE, Bartlett CM, Johnson KW, Levy PD, Noushmehr H, Lee IY. Machine Learning Applications in the Neuro ICU: A Solution to Big Data Mayhem? *Front Neurol* 2020; **11**: 554633 [PMID: 33162926 DOI: 10.3389/fneur.2020.554633]

23 **Claassen J**, Doyle K, Matory A, Couch C, Burger KM, Velazquez A, Okonkwo JU, King JR, Park S, Agarwal S, Roh D, Megjhani M, Eliseyev A, Connolly ES, Rohaut B. Detection of Brain Activation in Unresponsive Patients with Acute Brain Injury. *N Engl J Med* 2019; **380**: 2497-2505 [PMID: 31242361 DOI: 10.1056/NEJMoa1812757]

24 **Struck AF**, Rodriguez-Ruiz AA, Osman G, Gilmore EJ, Haider HA, Dhakar MB, Schrettner M, Lee JW, Gaspard N, Hirsch LJ, Westover MB; Critical Care EEG Monitoring Research Consortium (CCERMRC). Comparison of machine learning models for seizure prediction in hospitalized patients. *Ann Clin Transl Neurol* 2019; **6**: 1239-1247 [PMID: 31353866 DOI: 10.1002/acn3.50817]

25 **Koren JP**, Herta J, Fürbass F, Pirker S, Reiner-Deitemyer V, Riederer F, Flechsenhar J, Hartmann M, Kluge T, Baumgartner C. Automated Long-Term EEG Review: Fast and Precise Analysis in Critical Care Patients. *Front Neurol* 2018; **9**: 454 [PMID: 29973906 DOI: 10.3389/fneur.2018.00454]

26 **Yu Y**, Guo D, Lou M, Liebeskind D, Scalzo F. Prediction of Hemorrhagic Transformation Severity in Acute Stroke From Source Perfusion MRI. *IEEE Trans Biomed Eng* 2018; **65**: 2058-2065 [PMID: 29989941 DOI: 10.1109/TBME.2017.2783241]

27 **Raj R**, Luostarinen T, Pursiainen E, Posti JP, Takala RSK, Bendel S, Konttila T, Korja M. Machine learning-based dynamic mortality prediction after traumatic brain injury. *Sci Rep* 2019; **9**: 17672 [PMID: 31776366 DOI: 10.1038/s41598-019-53889-6]

28 **Miyagawa T**, Sasaki M, Yamaura A. Intracranial pressure based decision making: Prediction of suspected increased intracranial pressure with machine learning. *PLoS One* 2020; **15**: e0240845 [PMID: 33085690 DOI: 10.1371/journal.pone.0240845]

29 **Swiercz M**, Mariak Z, Krejza J, Lewko J, Szydlik P. Intracranial pressure processing with artificial neural networks: prediction of ICP trends. *Acta Neurochir (Wien)* 2000; **142**: 401-406 [PMID: 10883336 DOI: 10.1007/s007010050449]

30 **Megjhani M**, Alkhachroum A, Terilli K, Ford J, Rubinos C, Kromm J, Wallace BK, Connolly ES, Roh D, Agarwal S, Claassen J, Padmanabhan R, Hu X, Park S. An active learning framework for enhancing identification of non-artifactual intracranial pressure waveforms. *Physiol Meas* 2019; **40**: 015002 [PMID: 30562165 DOI: 10.1088/1361-6579/aaf979]

31 **Tanioka S**, Ishida F, Nakano F, Kawakita F, Kanamaru H, Nakatsuka Y, Nishikawa H, Suzuki H; pSEED group. Machine Learning Analysis of Matricellular Proteins and Clinical Variables for Early Prediction of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage. *Mol Neurobiol* 2019; **56**: 7128-7135 [PMID: 30989629 DOI: 10.1007/s12035-019-1601-7]

32 **Savin I**, Ershova K, Kurdyumova N, Ershova O, Khomenko O, Danilov G, Shifrin M, Zelman V. Healthcare-associated ventriculitis and meningitis in a neuro-ICU: Incidence and risk factors selected by machine learning approach. *J Crit Care* 2018; **45**: 95-104 [PMID: 29413730 DOI: 10.1016/j.jcrc.2018.01.022]

33 **Stapleton CJ**, Acharjee A, Irvine HJ, Wolcott ZC, Patel AB, Kimberly WT. High-throughput metabolite profiling: identification of plasma taurine as a potential biomarker of functional outcome after aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2019; 1-8 [PMID: 31756713 DOI: 10.3171/2019.9.JNS191346]

34 **Stell A**, Sinnott R, Jiang J, Donald R, Chambers I, Citerio G, Enblad P, Gregson B, Howells T, Kiening K, Nilsson P, Ragauskas A, Sahuquillo J, Piper I. Federating distributed clinical data for the prediction of adverse hypotensive events. *Philos Trans A Math Phys Eng Sci* 2009; **367**: 2679-2690 [PMID: 19487204 DOI: 10.1098/rsta.2009.0042]

35 **Badash I**, Burtt K, Solorzano CA, Carey JN. Innovations in surgery simulation: a review of past, current and future techniques. *Ann Transl Med* 2016; **4**: 453 [PMID: 28090509 DOI: 10.21037/atm.2016.12.24]

36 **Cooper MA**, Ibrahim A, Lyu H, Makary MA. Underreporting of robotic surgery complications. *J Healthc Qual* 2015; **37**: 133-138 [PMID: 23980819 DOI: 10.1111/jhq.12036]

37 **Liu VX**. The future of AI in critical care is augmented, not artificial, intelligence. *Crit Care* 2020; **24**: 673 [PMID: 33267905 DOI: 10.1186/s13054-020-03404-5]

38 **Bruynseels K**, Santoni de Sio F, van den Hoven J. Digital Twins in Health Care: Ethical Implications of an Emerging Engineering Paradigm. *Front Genet* 2018; **9**: 31 [PMID: 29487613 DOI: 10.3389/fgene.2018.00031]

39 **Andrews PS**, Polack FAC, Sampson AT, Scott L, Coles M. Simulating biology: towards understanding what the simulation shows. 2008. [cited 1 February 2021]. Available from: https://core.ac.uk/display/13611

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ORIGINAL ARTICLE

Retrospective Study

Emergency service results of central venous catheters: Single center, 1042 patients, 10-year experience

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Abstract

BACKGROUND

Central venous catheterization is currently an important procedure in critical care. Central catheterization has important advantages in many clinical situations. It can also lead to different complications such as infection, hemorrhage, and thrombosis. It is important to investigate critically ill patients undergoing catheterization.

AIM

To evaluate the characteristics, such as hospitalization, demographic characteristics, post-catheterization complications, and mortality relationships, of patients in whom a central venous catheter was placed in the emergency room.

METHODS

A total of 1042 patients over the age of 18 who presented to the emergency department between January 2005 and December 2015 were analyzed retrospectively. The patients were divided into three groups, jugular, subclavian, and femoral, according to the area where the catheter was inserted. Complications related to catheterization were determined as pneumothorax, guidewire problems, bleeding, catheter site infection, arterial intervention, and sepsis. Considering the treatment follow-up of the patients, three groups were formed as outpatient treatment, hospitalization, and death.

RESULTS

The mean age of the patients was 60.99 ± 19.85 years; 423 (40.6%) of them were women. Hospitalization time was 11.89 ± 16.38 d. There was a significant correlation between the inserted catheters with gender (P = 0.009) and hospitalization time (P = 0.040). Also, blood glucose, blood urea nitrogen, creatinine, and

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serum potassium values among the biochemical values of the patients who were catheterized were significant. A significant association was observed in the analysis of patients with complications that develop according to the catheter region (P = 0.001) and the outcome stage (P = 0.001). In receiver operating characteristic curve analysis of hospitalization time and mortality area under curve was 0.575, the 95% confidence interval was 0.496-0.653, the sensitivity was 71%, and the specificity was 89% (P = 0.040).

CONCLUSION

Catheter location and length of stay are important risk factors for catheter-borne infections. Because the risk of infection was lower than other catheters, jugular catheters should be preferred at entry points, and preventive measures should be taken by monitoring patients closely to reduce hospitalization infections.

Key Words: Emergency service; Central venous catheter; Complications; Infection; Mortality

Core Tip: A total of 1042 patients were included in this retrospective study. All central venous catheters were inserted in the emergency room. This study included 10 years of experience in our emergency department. In receiver operating characteristic curve analysis of hospitalization time and mortality, sensitivity was 71%, and specificity was 89% (P = 0.040). Complications in the subclavian vein and femoral vein were observed more frequently in the long term. Jugular vein catheterization can be preferred primarily due to the difficulties in application and due to the low number of complications.

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INTRODUCTION

Emergency services are dynamic clinics where acute and emergency aspects of diseases and injuries affecting patients of all age groups are prevented. Resuscitation, primary care, diagnosis, and treatment of emergency cases are performed. Due to the nature of acute illnesses and injuries and their independence from each other, when they will come to emergency services and their number cannot be predicted[1]. Acute procedures should be done as soon as possible in terms of the density, variety, and patient circulation of emergency services.

Intravenous applications in emergency rooms act as a lifeline in saving the life of the patient. For this reason, the process must be done quickly and safely. In a study conducted on patients with penetrating injuries in the emergency department, timely and effective intravenous interventions were reported to increase survival rates[2].

Central venous catheterization (CVC) is an important intervention that is widely used today. Emergency services have a large variety of patient populations where central venous interventions are frequently applied. CVC is necessary for the use of vasoactive or irritant drugs, in insufficient peripheral intravenous routes, rapid infusion of intravenous fluids, parenteral alimentation, frequent therapeutic plasmapheresis, and transvenous pacemaker placement. In addition, CVC is used for hemodialysis and hemodynamic monitoring during major surgery[3].

A central venous catheter is to be placed percutaneously. The main routes of catheterization are the internal jugular vein (IJV), subclavian vein (SCV), and femoral vein (FV). The placement of a catheter in the IJV is gaining in popularity and is preferred in children[4]. Various complications may develop in CVC, such as pneumothorax, hemothorax, venous thrombosis, vertebral and cervical artery injuries, artery puncture, bleeding, arrhythmia, catheter dysfunction such as catheter blockage or

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catheter breakage, infection, cardiac tamponade, respiratory tract obstruction, and chylothorax[5,6].

Each catheter region to be used has its advantages and disadvantages. IJV catheterization is often used in intensive care units on mechanically ventilated comatose patients. SCV catheterization is not preferred in these patients due to the risk of sudden pneumothorax[7]. The most important disadvantage of IJV catheterization is the difficulty of detecting the skin and restricting neck movements. The risk of pneumothorax, hemothorax, and vena cava superior injury is much less. At the same time, the development of thrombosis and narrowing of the IJV is much less due to the lack of catheter angulation, which is monitored in the SCV[8].

The aim of this study was to analyze the different catheter insertion sites, diagnoses, complications, length of hospitalization, catheter-related local infection, and bacteremia in terms of morbidity and mortality in patients who were followed up in the emergency service.

MATERIALS AND METHODS

Study design and population

In this retrospective study, 1042 patients over 18-years-old who were admitted to the emergency room between January 2005 and December 2015 were analyzed. CVC was implanted in patients whose general condition was poor, whose vascular access could not be opened in the emergency room, who needed dialysis and fluid resuscitation, who suffered traffic accidents, falls, burns, malignancy, or acute and chronic renal failure, and who needed blood or cardiopulmonary resuscitation. The exclusion criteria were applied to all patients with severe bleeding diathesis and an indication other than infection in the area where the catheter was to be placed. All patients were divided into three groups: jugular, subclavian, and femoral according to the area of the catheter placed. These catheters were divided into right and left. Seven groups were formed according to complications after catheterization: pneumothorax, guidewire problems, bleeding, catheter location infection, arterial interference, sepsis, and no complications. Patients who were planned to have a catheter application were divided into subgroups according to their diagnosis. The subgroups were renal diseases (acute and chronic renal failure), respiratory diseases (asthma, chronic obstructive pulmonary diseases, pulmonary embolism), endocrine diseases (hypoglycemia, diabetic ketoacidosis, hyperosmolar coma, thyroid crises), multiple organ failure, gastrointestinal bleeding and perforations, cerebrovascular diseases (cerebrovascular infarcts, intraparenchymal hemorrhages, epidural and subdural hemorrhages, cerebral edema, subarachnoid hemorrhages), trauma to the thorax (thoracic open injury, severe pneumothoraces, severe lung parenchymal injuries), traffic accidents (inside and outside the vehicle), malignancies in poor general condition, life-threatening gunshot injuries, cardiac diseases (myocardial infarction, heart failure, cardiac tamponade, cardiomyopathies), cardiovascular diseases (aortic dissection and aneurysms), severe injuries as a result of falls, second and third-degree burns with a large surface area, extremity amputation, penetrating-cutting tool injuries, and cardiopulmonary resuscitation. It could be done in more groups, but the most common diagnoses requiring catheter indication were included in the emergency department.

Sixteen groups were also identified according to the services where catheterized patients were hospitalized. These services were emergency services, infectious diseases, general internal medicine, nephrology, gastroenterology, intensive care unit, cardiology, neurosurgery, thoracic surgery, chest diseases, general surgery, cardiovascular surgery, neurosurgery, plastic surgery, burn unit, and neurology services.

Patients were observed from hospitalization until discharge. Outpatients were followed up retrospectively with an automation system for 3 mo after they were discharged, and those who did not come to the hospital were questioned by phone. Diagnoses, admission dates, contact information, demographic, clinical, and laboratory data are included in the registry system of our hospital. As a result, all patients were reached *via* call and/or hospital records.

Central venous catheter

Kits prepared for central venous catheter application in the emergency department were used. Components of these kits included: The needle included an injector to allow passage of the guidewire, double or triple catheter, guidewire, plastic sheath in which the guidewire was placed, dilator, 3/0 silk sharp needle suture, and scalpel. A

central venous catheter procedure was performed under local anesthesia. The patient was placed in the supine position. The jugular vein catheter was positioned with the head slightly down. For the SCV catheter, the arms were extended to the sides parallel to the body. For the FV catheter, the legs were kept open at a certain angle. During the procedure, the patient was monitored, and heart rhythm was followed. The sterility of the area where the catheter will be applied was provided with 10% povidone-iodine. Lidocaine was used for local anesthesia. The Seldinger technique was used for central venous catheter application[9]. Main lines of central venous catheter application after anesthesia was achieved included: (1) sterilizing the procedure area; (2) proper positioning of the thick needle to which the guidewire will be sent; (3) inserting the guidewire into the vein lumen by applying slight negative pressure; (4) advancing the guidewire into the vein lumen; (5) dilating the path through which the catheter will pass; (6) inserting the catheter into the vein with the help of a guidewire; (7) adequate progression and fixation of the catheter in the vein; and (8) closing in a sterile manner. Lung radiography and ultrasonography were performed for central venous catheter complications.

Catheter-related infection was determined according to the "Centers for Disease Control" criteria[10]. Catheter tip colonization was accepted if more than 15 colony-forming units microorganisms were produced from the catheter tip. Local signs for catheter-induced local infection (induration, edema, heat increase, purulent yeast arrival) and the reproduction of microorganisms in catheter tip culture were noted.

Criteria used in determining the location of the central venous catheter

In the emergency department, ultrasonography was not commonly used until 2018. For this reason, none of the 1042 patients could be subjected to catheter placement accompanied by ultrasonography. Accompanied by ultrasonography, we were unable to learn about complications that may occur as a result of catheter placement. But for catheter placement, all patients were applied with some criteria. These criteria are as follow.

Jugular catheters: Elderly, cachectic, superficial vein structure, lack of coagulopathy barrier, lack of local wound infection, low risk of pneumothorax, rapid venous return, and direct compression in bleeding. Right or left catheter placement was performed according to the current condition of the patient and the experience of the clinician.

Subclavian catheters: Obesity, the dressing was comfortable, the placement procedure was possible while ensuring airway control, there was no local infection, no coagulopathy, and the right or left catheter was placed according to the experience of the clinician.

Femoral catheters: Fast intervention with high success rate, no local infection, no coagulopathy, no division during cardiopulmonary resuscitation and/or intubation, no risk of pneumothorax, no Trendelenburg position, cachectic patients and according to the experience of the clinician, right or left catheters were placed. However, due to the current location of the inguinal region, jugular or subclavian catheters were preferred more because of the high risk of infection, although sterility was taken into consideration.

Laboratory design: Hemogram and biochemical blood samples of the patients were taken at the emergency service. Hemogram was measured using Sysmex DI-60 CBC Analyzer (Istanbul, Turkey). Biochemistry was analyzed by Beckman Coulter Automated AU-680 (Beckman Coulter, Inc., Fullerton, CA, United States). Hemogram and biochemistry results were studied between 45-60 min.

Statistical analysis

The data obtained from the study were analyzed with the SPSS 20 (SPSS Inc., Chicago, IL, United States) package program. Kolmogorov-Smirnov test was performed while investigating the normal distributions of the variables. Descriptive statistics were presented as mean ± SD or median (minimum-maximum) for continuous variables and as the number of cases and percentage (%) for nominal variables. When examining the differences between groups, Mann-Whitney *U* and Kruskal-Wallis H tests were used because the variables did not come from the normal distribution. ^{2} analysis was used when examining the relationships between groups of nominal variables. Receiver operating characteristic curve analysis was performed to predict the development of mortality. While interpreting the results, values below the significance level of 0.05 were considered statistically significant.

RESULTS

The mean age of the patients was 60.99 ± 19.85 years (minimum 18-maximum 99); 423 (40.6%) of them were women. The mean age of jugular vein catheter patients was 60.74 ± 20.20 years, and 339 (40%) were female. The mean age of SCV catheter patients was 59.66 ± 19.17 years, and 42 (27.3%) were female. The mean age of FV catheter patients was 63.67 ± 18.57 years and 42 (42%) were women. Hospitalization time was 11.89 ± 16.38 d. The patients who were catheterized were not statistically significant with age ($P = 0.939$), but there was a significant correlation with gender ($P = 0.009$) and hospitalization time ($P = 0.040$). Also, blood glucose, blood urea nitrogen, creatinine, and serum potassium were statistically significant from the biochemical values of the patients who were catheterized. The relationship with other biochemical values could not be determined. Among the hemogram parameters, it was statistically significant with hemoglobin and mean corpuscular hemoglobin concentration, and no correlation was found with other values (Table 1).

In the analysis of the patients by catheter site, gender ($P = 0.004$), developing complications ($P = 0.009$), and final decision stage ($P = 0.001$) were statistically significant. While 174 (16.7%) of all patients were treated on an outpatient basis, 783 (75.1%) of them were found to be cured, and 85 (8.2%) died ($P = 0.001$, Table 2).

In the analysis of patients with their diagnosis according to the catheterized region, in general, the right IJV catheter was inserted most often. In addition, the right FV in multiple organ failure, the left SCV in chest injuries, burns, piercing-cutting tool injuries, and cardiopulmonary resuscitation, and the right SCV in cardiovascular diseases were the most common catheter-inserted vein (Table 3).

The analysis of the patients according to the services they received while hospitalized after being catheterized is shown in Table 4.

In receiver operating characteristic curve analysis of hospitalization time and mortality, the area under curve was 0.575, the 95% confidence interval was 0.496-0.653, the sensitivity was 71%, and the specificity was 89% ($P = 0.001$) (Figure 1).

DISCUSSION

Intravenous catheters, one of the indispensable tools in modern medical practices, are applied for specific purposes and can be used for a long time. Although central venous catheters provide great benefits for patients, they also cause significant mortality and morbidity due to both mechanical and infectious complications[11,12]. In emergencies and critical patient follow-up, CVC is often needed. However, there are important points to be considered in CVC. First of all, it should be preferred to use a central vein with a large flow rate and high current. For this purpose, percutaneous IJV, SCV, and FV are used in CVC[4]. Right IJV is preferred primarily because of its straight connection with the superior vena cava and its short distance to the right atrium[7]. Left IJV should be the next choice because it reaches the superior vena cava by angulation twice, and catheterization is technically difficult. If there are coagulation and bleeding disorders, SCV catheterization is high risk, and in these cases, extrathoracic veins such as IJV or FV should be used[3,7,8]. Mickley[8] stated that the right IJV should be used if possible for central venous interventions and hemodialysis catheters. Central vein catheterization is a generally accepted protocol using the original Seldinger technique[9]. The Seldinger technique was used in all cases, and the rules of asepsis were adhered to. Right IJV was observed in 56.7% of the cases, left IJV in 14.8%, right SCV in 6.5%, left SCV in 8.4%, right FV in 7.4%, and left FV in 6.1%.

CVC can cause some complications. Early complications include arterial puncture, development of hematoma, nerve injury, pneumothorax, hemothorax, difficulty in cannulation, and arrhythmia. No complications were observed in 92.9% of our patients, most of whom had IJV intervention. In addition to expected complications such as pneumothorax and hemothorax, complications such as brachial plexus injury due to SCV catheterization or massive retroperitoneal hemorrhage due to femoral catheterization can be seen[13,14]. Pneumothorax was seen in 4 (0.4%) cases, one right subclavian and three left subclavian cases. All of these patients were cachectic and in poor general condition. Catheter dysfunction is caused by catheter malposition, catheter kinking, or catheter compression[15,16]. Bending and breaking of the guidewire in the vein was detected in a total of 2 (0.2%) patients, one in the left SCV and the other in the right FV. In preventing early catheter dysfunction, IJV catheterization may be an advantage in priority. In total, 8 (0.8%) of the patients had bleeding, 30 patients (2.9%) had artery puncture, 1 patient had hematoma, and 2 patients had

Table 1 Basal and laboratory features of the inserted catheters

Catheter area inserted					
	All patients, *n* = 1042, mean ± SD	**Jugular, *n* = 743, mean ± SD**	**Subclavian, *n* = 155, mean ± SD**	**Femoral, *n* = 144, mean ± SD**	***P* value**
Baseline characteristics					
Age, yr	60.99 ± 19.85	60.74 ± 20.20	59.66 ± 19.17	63.67 ± 18.57	0.939
Sex, female/male	423/619	339/449	42/112	42/58	**0.009**
Hospitalization time	11.89 ± 16.38	12.50 ± 16.03	11.00 ± 20.08	9.73 ± 13.39	**0.040**
Laboratory finding					
Biochemistry					
BS, mg/dL	139.45 ± 101.56	145.21 ± 112.63	120.35 ± 55.74	130.30 ± 72.49	0.008
BUN, mg/dL	42.77 ± 41.29	51.11 ± 44.40	19.65 ± 13.91	24.58 ± 26.42	0.001
Creatinine, mg/dL	2.62 ± 2.89	3.20 ± 3.14	0.99 ± 0.68	1.37 ± 1.68	0.001
TBIL, mg/dL	0.87 ± 0.84	0.82 ± 0.63	0.80 ± 0.88	1.22 ± 1.43	0.485
AST, mg/dL	37.65 ± 47.22	32.56 ± 25.60	40.04 ± 60.05	61.38 ± 90.77	0.508
ALT, mg/dL	35.81 ± 49.37	30.31 ± 26.18	38.58 ± 67.59	61.21 ± 91.95	0.710
ALP, mg/dL	108.57 ± 64.10	104.95 ± 56.71	104.66 ± 59.33	131.48 ± 93.90	0.569
Na, mmol/L	138.61 ± 5.38	138.68 ± 5.33	138.22 ± 5.07	138.68 ± 5.96	0.125
K, mmol/L	5.00 ± 1.03	5.13 ± 1.10	5.07 ± 0.71	4.79 ± 0.70	0.027
Cl, mmol/L	100.23 ± 6.23	100.18 ± 6.11	100.41 ± 6.95	100.29 ± 6.04	0.778
Amylase	89.98 ± 49.88	87.93 ± 47.66	91.64 ± 53.25	98.78 ± 56.30	0.419
CRP, mg/dL	4.44 ± 8.12	3.53 ± 5.14	4.32 ± 7.65	9.26 ± 15.90	0.925
Hemogram					
WBC, × 10^3/UL	10.57 ± 4.51	10.26 ± 3.59	10.32 ± 4.05	12.49 ± 7.72	0.228
Hb, g/dL	13.77 ± 2.07	13.63 ± 2.12	14.09 ± 1.77	14.16 ± 1.98	0.017
Hct, %	42.17 ± 6.62	42.07 ± 6.78	42.23 ± 5.80	42.62 ± 6.65	0.737
MCV, fL	87.74 ± 6.29	87.71 ± 6.42	87.45 ± 6.18	88.24 ± 5.70	0.927
MCH, pg	29.37 ± 2.36	29.30 ± 2.41	29.48 ± 2.29	29.67 ± 2.20	0.905
MCHC, g/dL	33.25 ± 1.36	33.19 ± 1.37	33.47 ± 1.29	33.29 ± 1.36	0.002
RDW, %	14.69 ± 1.73	14.74 ± 1.79	14.45 ± 1.50	14.66 ± 1.61	0.082
PLT, × 103/μL	248.22 ± 80.14	248.71 ± 76.33	256.88 ± 76.01	236.42 ± 100.38	0.073
MPV, fL	8.48 ± 1.01	8.54 ± 1.03	8.33 ± 1.06	8.34 ± 0.86	0.085

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase test; AST: Aspartate aminotransferase test; BS: Blood sugar; BUN: Blood urea nitrogen; Cl: Chlorine; CRP: C-reactive protein; Hb: Hemoglobin; Hct: Hematocrit; K: Potassium; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume; MPV: Mean platelet volume; Na: Sodium; PLT: Platelet; RDW: Red cell distribution width; SD: Standard deviation; TBIL: Total bilirubin; WBC: White blood cell.

difficulty catheterizing. In similar studies, the incidence of carotid artery puncture was reported between 2.0%-9.9% during catheterization of IJV[5]. Most of the difficulties in arterial puncture and cannulation observed in our catheterization-related cases were obesity, short neck, elderly, and poor general condition as the main cause of these early complications.

During jugular catheterization, complications such as Horner Syndrome, arrhythmia, and cardiac tamponade have been reported, as well as the development of carotid-jugular arteriovenous fistula due to carotid puncture[17,18]. In a total of 4 (0.4%) cases, no other complications were observed except arrhythmia. It is recommended to monitor the patient during the jugular site catheterization and to take a chest radiograph after the application[19]. Both examinations are routinely performed

Table 2 Analysis of the inserted catheter area according to gender, complication, and final situation

	Catheter area inserted						Total, *n* (%)	*P* value
	R jugular, *n* (%)	L jugular, *n* (%)	R subclavian, *n* (%)	L subclavian, *n* (%)	R femoral, *n* (%)	L femoral, *n* (%)		
Gender								
Female	248 (42.0)	73 (47.4)	20 (29.4)	23 (26.1)	30 (39.0)	29 (45.3)	423 (40.6)	0.009
Male	343 (58.0)	81 (52.6)	48 (70.6)	65 (73.9)	47 (61.0)	35 (54.7)	619 (59.4)	
Complication								
No	583 (98.6)	149 (96.8)	63 (92.6)	75 (85.2)	49 (63.6)	46 (71.9)	965 (92.6)	0.001
Pntx	0	0	1 (1.5)	3 (3.4)	0	0	4 (0.4)	
GW	0	0	0	0	1 (1.3)	1 (1.6)	2 (0.2)	
Bleeding	2 (0.3)	0	0	4 (4.5)	1 (1.3)	1 (1.6)	8 (0.8)	
WI	2 (0.3)	1 (0.6)	1 (1.5)	1 (1.1)	2 (2.6)	6 (9.4)	13 (1.2)	
AI	4 (0.7)	4 (2.6)	2 (2.9)	3 (3.4)	11 (14.3)	3 (4.7)	27 (2.6)	
Sepsis	0	0	1 (1.5)	2 (2.3)	13 (16.9)	7 (10.9)	23 (2.2)	
Decision								
OPT	104 (17.6)	28 (18.2)	12 (17.6)	14 (15.9)	9 (11.7)	7 (10.7)	174 (16.7)	0.001
DWH	484 (81.9)	121 (78.6)	46 (67.6)	58 (63.6)	35 (45.5)	41 (64.1)	783 (75.1)	
Mortality	3 (0.5)	5 (3.2)	10 (14.7)	18 (20.5)	33 (42.9)	16 (25.0)	85 (8.2)	
Total	591 (100)	154 (100)	68 (100)	88 (100)	77 (100)	64 (100)	1042 (100)	

AI: Arterial intervention; DWH: Discharged with healing; GW: Guide wire; L: Left; Pntx: Pneumothorax; OPT: Outpatient treatment; R: Right; WI: Wound infection.

in our cases. Also, in cases with arrhythmia, the guidewire was withdrawn to a certain extent, the procedure was interrupted, and major complications were prevented.

The average staying time of temporary catheters should not exceed 3-4 wk for IJV and SCV catheters and 2 wk for femoral catheters[5]. The average length of stay in our study did not exceed 2 wk. The length of stay of the catheter is associated with both thrombotic complications and the risk of infection[20].

In the study of Cook *et al*[21], it was stated that changing catheters at short intervals did not decrease the frequency of colonization and infection. Because catheter insertion is a traumatic procedure and there is a risk that asepsis conditions may deteriorate during catheter insertion, installing a new catheter in itself poses a risk of catheter-related infection. It is known that there is a directly proportional relationship between catheter insertion time and catheter colonization and catheter-related infection[22,23]. Chen *et al*[24] found that the stay of the catheter for more than 7 d was significant in terms of catheter-related infection.

Infections developing in CVC for various reasons lead to very serious complications including patient mortality[25]. Early infection is associated with contamination during catheter insertion, skin infection, or catheter pathway infection. Late infection is often accompanied by endoluminal catheter contamination[26]. Two types of infections are observed: local infection and systemic infections. *Staphylococcus aureus* (*S. aureus)* and *S. epidermiditis* are the most common microorganisms isolated during catheter-related bacteremia. This risk increases in the presence of wound infection. The risk of infection is higher with FV catheters than with SCV and IJV catheters[27]. In our study, wound infection due to catheters was detected in 13 (1.2%) cases. Localized infection findings were observed in 8 (0.7%) FV, 3 (0.3%) IJV, and 2 (0.2%) SCV. Although *S. aureus* and *S. epidermiditis* grew in the samples taken from the wound site, there was no growth in the samples taken from the catheter tip. Blood cultures were not routinely sent from the patients. We think that there was no growth in the catheter tip cultures, care for sterility while inserting the catheter, careful and regular dressing of the insertion site, and not using the catheters for more than 3 wk.

Table 3 Analysis of inserted catheter sites according to diseases

Diagnosis	Catheter area inserted						Total, *n* (%)
	R jugular, *n* (%)	L jugular, *n* (%)	R subclavian, *n* (%)	L subclavian, *n* (%)	R femoral, *n* (%)	L femoral, *n* (%)	
Renal diseases	228 (38.5)	43 (27.9)	1 (1.5)	2 (2.3)	6 (7.8)	5 (7.8)	285 (27.3)
Respiratory diseases	45 (7.6)	8 (5.1)	3 (4.4)	3 (3.4)	16 (20.8)	6 (9.4)	81 (7.8)
Endocrine diseases	34 (5.8)	7 (4.5)	1 (1.5)	0	4 (5.2)	0	46 (4.4)
Multiple organ insufficiency	0	0	1 (1.5)	2 (2.3)	12 (15.6)	7 (10.9)	22 (2.1)
Gastrointestinal system bleeding	56 (9.5)	12 (7.8)	2 (2.9)	0	0	3 (4.7)	73 (7.0)
Gastrointestinal system perforations	27 (4.6)	2 (1.3)	2 (2.9)	0	5 (6.5)	1 (1.6)	37 (3.6)
Cerebrovascular diseases	61 (10.3)	16 (10.4)	0	1 (1.1)	4 (5.2)	3 (4.7)	85 (8.2)
Thoracic traumas	1 (0.2)	0	7 (10.3)	14 (15.9)	0	0	22 (2.1)
Traffic accidents	12 (2.0)	7 (4.5)	1 (1.5)	2 (2.3)	0	0	22 (2.1)
Malignancies	30 (5.1)	7 (4.5)	4 (5.9)	1 (1.1)	4 (5.2)	4 (6.3)	50 (4.8)
Firearm injury	5 (0.8)	3 (1.9)	3 (4.4)	4 (4.5)	1 (1.3)	1 (1.6)	17 (1.6)
Cardiac diseases	39 (6.6)	22 (14.3)	1 (1.5)	1 (1.1)	5 (6.5)	13 (20.3)	81 (7.8)
Cardiovascular diseases	1 (0.2)	2 (1.3)	3 (4.4)	3 (3.4)	6 (7.8)	0	15 (1.4)
Falls	26 (4.4)	15 (9.7)	12 (17.6)	7 (8.0)	3 (3.9)	6 (9.4)	69 (6.6)
Burns	22 (3.7)	9 (5.8)	18 (26.5)	27 (30.7)	8 (10.4)	12 (18.8)	96 (9.2)
Amputation	1 (0.2)	1 (0.6)	0	2 (2.3)	0	0	4 (0.4)
Penetrating tool injury	3 (0.5)	0	8 (11.8)	11 (12.5)	1 (1.3)	1 (1.6)	24 (2.3)
Cardiopulmonary resuscitation	0	0	1 (1.5)	8 (9.1)	2 (2.6)	2 (3.1)	13 (1.2)
Total	591 (100)	154 (100)	68 (100)	88 (100)	77 (100)	64 (100)	1042 (100)

L: Left; R: Right.

Blot *et al*[28] found that *S. aureus*, coagulase negative *Staphylococcus*, and *Pseudomonas aeruginosa* were the most frequently isolated agents in catheter-related infections and catheter colonization. Chen *et al*[24] often isolated Gram-positive cocci and yeasts in cases of catheter-related infection. In the study of Yapar *et al*[29], 14 of 97 patients using long-term CVC had a catheter-related infection, 28.5% of the agents were coagulase negative *Staphylococcus*, 21.4% *S. aureus*, 21.4% *Acinetobacter* species, and 14.5% *Klebsiella pneumoniae*. It has been reported that 7.1% are *Pseudomonas* species, and 7.1% are *Escherichia coli*. Although catheter-related blood infections vary according to the size of the hospital, the unit, and the type of catheter, studies have reported that it ranges between 2.5% and 14.5%[25]. In our study, sepsis developed due to infection in 23 (2.2%) patients. Most of these patients were detected in 13 (1.2%) cases in the right FV and 7 (0.7%) cases in the left FV. All of these cases consisted of obese, poor general condition, and intensive care patients. In 6 (0.6%) of these blood culture cases, *S. aureus*, 3 (0.3%) coagulase negative *Staphylococcus*, 2 (0.2%) *Pseudomonas aeruginosa*, 3 (0.3%) *Acinetobacter* species, 7 (0.7%) *Escherichia coli*, and 2 (0.2%) Gram-positive cocci were found to reproduce. While 174 (16.7%) of all patients were treated on an outpatient basis, 783 (75.1%) of them were found to be cured, and 85 (8.2%) died. The reason for the high mortality rate is that the general condition of patients with catheters inserted is poor, the coma score is low, and most patients need care.

CONCLUSION

CVC is an indispensable application especially for emergency services and brings with

Table 4 Analysis of the inserted catheter areas according to the services where the patients were hospitalized

Hospital services	Catheter area inserted						Total, *n* (%)
	R jugular, *n* (%)	L jugular, *n* (%)	R subclavian, *n* (%)	L subclavian, *n* (%)	R femoral, *n* (%)	L femoral, *n* (%)	
Emergency department	94 (15.9)	27 (17.5)	12 (17.6)	14 (15.9)	10 (13.0)	10 (15.6)	167 (16)
Infectious diseases service	11 (1.9)	2 (1.3)	1 (1.5)	1 (1.1)	3 (3.9)	4 (6.3)	22 (2.1)
General internal medicine service	173 (29.3)	45 (29.2)	5 (7.4)	1 (1.1)	9 (11.7)	8 (12.5)	241 (23.1)
Nephrology service	99 (16.8)	21 (13.6)	0	3 (3.4)	7 (9.1)	5 (7.8)	135 (13)
Gastroenterology service	29 (4.9)	7 (4.5)	0	0	0	2 (3.1)	38 (3.6)
Intensive care unit	40 (6.8)	10 (6.5)	13 (19.1)	17 (19.3)	31 (40.3)	20 (31.3)	131 (12.6)
Cardiology service	12 (2.0)	3 (1.9)	1 (1.5)	2 (2.3)	1 (1.3)	1 (1.6)	20 (1.9)
Brain surgery service	24 (4.1)	7 (4.5)	5 (7.4)	7 (8.0)	2 (2.6)	3 (4.7)	48 (4.6)
Thoracic surgery service	4 (0.7)	4 (2.6)	6 (8.8)	13 (14.8)	4 (5.2)	2 (3.1)	33 (3.2)
Chest diseases service	18 (3.0)	7 (4.5)	0	1 (1.1)	1 (1.3)	1 (1.6)	28 (2.7)
General surgery service	46 (7.8)	3 (1.9)	8 (11.8)	9 (10.2)	7 (9.1)	4 (6.3)	77 (7.4)
Cardiovascular surgery service	10 (1.7)	0	7 (10.3)	10 (11.4)	1 (1.3)	1 (1.6)	29 (2.8)
Orthopedics and traumatology service	10 (1.7)	13 (8.4)	10 (14.7)	6 (6.8)	0	2 (3.1)	41 (3.9)
Plastic and reconstructive surgery service	4 (0.7)	2 (1.3)	0	4 (4.5)	0	1 (1.6)	11 (1.1)
Neurology service	17 (2.9)	3 (1.9)	0	0	1 (1.3)	0	21 (2.0)
Total	591 (100)	154 (100)	68 (100)	88 (100)	77 (100)	64 (100)	1042 (100)

L: Left; R: Right.

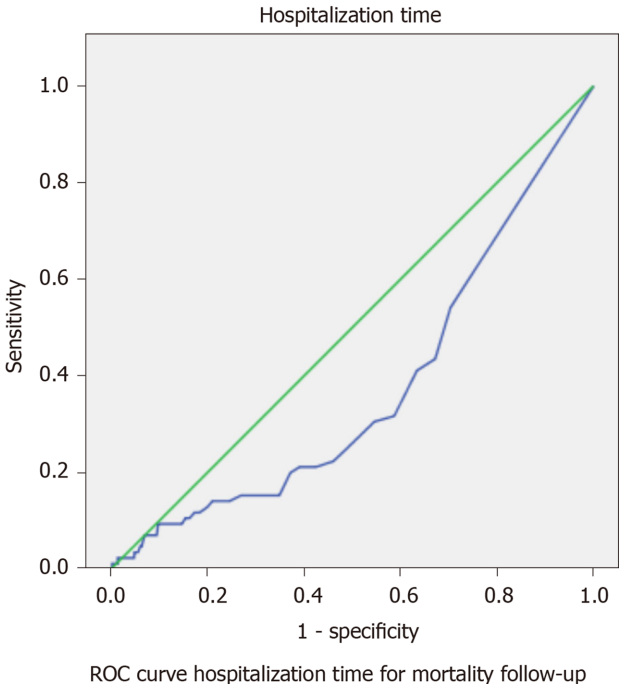

Figure 1 Mortality analysis of hospitalization time. ROC: Receiver operating characteristic.

it the risk of many complications. Complications in the subclavian and FVs are more common in long-term use. Jugular vein catheterization can be preferred primarily due to the difficulties in application and the low number of complications. In addition, prevention of risk factors with infection control policies and measures developed can significantly reduce catheter-related infection rates.

ARTICLE HIGHLIGHTS

Research background

Risk assessment in patients with a central venous catheter is necessary to prevent some unwanted consequences associated with invasive procedures.

Research motivation

The impact on the clinical, morbidity, and mortality of patients with central venous catheters in the emergency room population is worth investigating.

Research objectives

We aimed to determine whether there is a definite risk factor in short-term emergency room stay as the primary outcome of patients with central venous catheters and as a secondary outcome whether there is long-term morbidity and mortality at the time of hospitalization.

Research methods

In this study, 1042 patients who were admitted to the emergency department between 2005 and 2015 were analyzed, retrospectively. The patients in whom a central venous catheter was placed in the study were divided into three groups as jugular, subclavian, and femoral. Complications, diagnosis, and hospital stay after catheter insertion were evaluated.

Research results

The mean age of the patients was 60.99 ± 19.85 years; 423 (40.6%) of them were women. Hospitalization time was 11.89 ± 16.38 d. The mean age of the patients with jugular catheters was 60.74 ± 20.20 years, and 339 (40%) of them were women. The mean age of subclavian catheter patients was 59.66 ± 19.17 years, and 42 (27.3%) of them were women. In femoral catheters, the mean age was 63.67 ± 18.57 years, and 42 (42%) were women. There was a significant relationship between the inserted catheters with gender (P = 0.009) and hospitalization time (P = 0.040). , the biochemical values of the placed catheters were statistically significant with blood glucose, blood urea nitrogen, creatinine, and serum potassium. A significant association was observed in the analysis of patients according to complications (P = 0.001) and outcome stage (P = 0.001). While 174 (16.7%) of all patients were treated on an outpatient basis, 783 (75.1%) of them were found to be cured, and 85 (8.2%) died. In receiver operating characteristic curve analysis of hospitalization time and mortality, the area under curve was 0.575, the 95% confidence interval was 0.496-0.653, the sensitivity was 71%, and the specificity was 89% (P = 0.040).

Research conclusions

The jugular vein is safer and more comfortable for patient compliance between central venous catheters. Femoral vein catheters are at higher risk for infection. Changing central catheters frequently does not reduce the risk of infection and complications.

Research perspectives

Subclavian catheters have a high risk of hemopneumothorax in cachectic patients. Jugular catheters are safe. However, it is not preferred due to the discomfort of the patients and the limited neck movements. It is difficult to attach a jugular catheter to short and obese patients. Also, artery puncture is common. Femoral catheters are the group with the highest infection rate.

REFERENCES

1 **The European Emergency Medicine Core Curriculum**. Turkey Emergency Medicine Society,

European Society for Emergency Medicine Association (EUSEM), and the European Society for Emergency Medical Specialists (UEMS) Emergency Medicine Multidisciplinary Committee (EMMC) approved, use for the Core Curriculum Workgroup Document 2008. Brussels: Belgium, 2008
2 **Türkdemir AH**, Güleç MA, Eraslan S, Arıca F, Akkaya M, Giray F. Effectiveness of vascular access in penetrating injuries. *Academic Emerg Med J* 2007; **55**: 22-38
3 **Ruesch S**, Walder B, Tramèr MR. Complications of central venous catheters: internal jugular *vs* subclavian access--a systematic review. *Crit Care Med* 2002; **30**: 454-460 [PMID: 11889329 DOI: 10.1097/00003246-200202000-00031]
4 **Sznajder JI**, Zveibil FR, Bitterman H, Weiner P, Bursztein S. Central vein catheterization. Failure and complication rates by three percutaneous approaches. *Arch Intern Med* 1986; **146**: 259-261 [PMID: 3947185 DOI: 10.1001/archinte.146.2.259]
5 **McGee DC**, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med* 2003; **348**: 1123-1133 [PMID: 12646670 DOI: 10.1056/NEJMra011883]
6 **Mansfield PF**, Hohn DC, Fornage BD, Gregurich MA, Ota DM. Complications and failures of subclavian-vein catheterization. *N Engl J Med* 1994; **331**: 1735-1738 [PMID: 7984193 DOI: 10.1056/NEJM199412293312602]
7 **Lefrant JY**, Muller L, De La Coussaye JE, Prudhomme M, Ripart J, Gouzes C, Peray P, Saissi G, Eledjam JJ. Risk factors of failure and immediate complication of subclavian vein catheterization in critically ill patients. *Intensive Care Med* 2002; **28**: 1036-1041 [PMID: 12185422 DOI: 10.1007/s00134-002-1364-9]
8 **Mickley V**. Central venous catheters: many questions, few answers. *Nephrol Dial Transplant* 2002; **17**: 1368-1373 [PMID: 12147780 DOI: 10.1093/ndt/17.8.1368]
9 **SELDINGER SI**. Catheter replacement of the needle in percutaneous arteriography; a new technique. *Acta radiol* 1953; **39**: 368-376 [PMID: 13057644 DOI: 10.3109/00016925309136722]
10 **Garner JS**, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; **16**: 128-140 [PMID: 2841893 DOI: 10.1016/0196-6553(88)90053-3]
11 **Henderson DK**. Infections caused by percutaneous intravascular devices. In: Mandeli GL, Bennett JE, Dolin R. Principles and Practice of Infectious Diseases. 6th ed. Philadelphia: Churchill-Livingstone IIne, 2005: 3347-3362
12 **Polderman KH**, Girbes AJ. Central venous catheter use. Part 1: mechanical complications. *Intensive Care Med* 2002; **28**: 1-17 [PMID: 11818994 DOI: 10.1007/s00134-001-1154-9]
13 **Karakaya D**, Baris S, Güldogus F, Incesu L, Sarihasan B, Tür A. Brachial plexus injury during subclavian vein catheterization for hemodialysis. *J Clin Anesth* 2000; **12**: 220-223 [PMID: 10869922 DOI: 10.1016/s0952-8180(00)00144-6]
14 **Akata T**, Nakayama T, Kandabashi T, Kodama K, Takahashi S. Massive retroperitoneal hemorrhage associated with femoral vein cannulation. *J Clin Anesth* 1998; **10**: 321-326 [PMID: 9667349 DOI: 10.1016/s0952-8180(98)00036-1]
15 **Puri VK**, Carlson RW, Bander JJ, Weil MH. Complications of vascular catheterization in the critically ill. A prospective study. *Crit Care Med* 1980; **8**: 495-499 [PMID: 7418424 DOI: 10.1097/00003246-198009000-00004]
16 **Muhm M**, Sunder-Plassmann G, Apsner R, Pernerstorfer T, Rajek A, Lassnigg A, Prokesch R, Derfler K, Druml W. Malposition of central venous catheters. Incidence, management and preventive practices. *Wien Klin Wochenschr* 1997; **109**: 400-405 [PMID: 9226858]
17 **Droll KP**, Lossing AG. Carotid-jugular arteriovenous fistula: case report of an iatrogenic complication following internal jugular vein catheterization. *J Clin Anesth* 2004; **16**: 127-129 [PMID: 15110376 DOI: 10.1016/j.jclinane.2003.06.003]
18 **Taskapan H**, Oymak O, Dogukan A, Utas C. Horner's syndrome secondary to internal jugular catheterization. *Clin Nephrol* 2001; **56**: 78-80 [PMID: 11499663]
19 **Gladwin MT**, Slonim A, Landucci DL, Gutierrez DC, Cunnion RE. Cannulation of the internal jugular vein: is postprocedural chest radiography always necessary? *Crit Care Med* 1999; **27**: 1819-1823 [PMID: 10507604 DOI: 10.1097/00003246-199909000-00019]
20 **Crain MR**, Mewissen MW, Ostrowski GJ, Paz-Fumagalli R, Beres RA, Wertz RA. Fibrin sleeve stripping for salvage of failing hemodialysis catheters: technique and initial results. *Radiology* 1996; **198**: 41-44 [PMID: 8539402 DOI: 10.1148/radiology.198.1.8539402]
21 **Cook D**, Randolph A, Kernerman P, Cupido C, King D, Soukup C, Brun-Buisson C. Central venous catheter replacement strategies: a systematic review of the literature. *Crit Care Med* 1997; **25**: 1417-1424 [PMID: 9267959 DOI: 10.1097/00003246-199708000-00033]
22 **Crump JA**, Collignon PJ. Intravascular catheter-associated infections. *Eur J Clin Microbiol Infect Dis* 2000; **19**: 1-8 [PMID: 10706172 DOI: 10.1007/s100960050001]
23 **Fraenkel DJ**, Rickard C, Lipman J. Can we achieve consensus on central venous catheter-related infections? *Anaesth Intensive Care* 2000; **28**: 475-490 [PMID: 11094662 DOI: 10.1177/0310057X0002800501]
24 **Chen HS**, Wang FD, Lin M, Lin YC, Huang LJ, Liu CY. Risk factors for central venous catheter-related infections in general surgery. *J Microbiol Immunol Infect* 2006; **39**: 231-236 [PMID: 16783454]
25 **Ulusoy S**, Akan H, Arat M, Baskan S, Bavbek S, Çakar N, Çetinkaya ŞY, Somer A, Şimşek YS. Intravascular Catheter Infections Prevention Guide. *Turkish J Hosp Infect* 2005; **9**: 5-9
26 **McKinley S**, Mackenzie A, Finfer S, Ward R, Penfold J. Incidence and predictors of central venous

catheter related infection in intensive care patients. *Anaesth Intensive Care* 1999; **27**: 164-169 [PMID: 10212713 DOI: 10.1177/0310057X9902700206]

27 **Charalambous C**, Swoboda SM, Dick J, Perl T, Lipsett PA. Risk factors and clinical impact of central line infections in the surgical intensive care unit. *Arch Surg* 1998; **133**: 1241-1246 [PMID: 9820357 DOI: 10.1001/archsurg.133.11.1241]

28 **Blot F**, Nitenberg G, Chachaty E, Raynard B, Germann N, Antoun S, Laplanche A, Brun-Buisson C, Tancrède C. Diagnosis of catheter-related bacteraemia: a prospective comparison of the time to positivity of hub-blood *vs* peripheral-blood cultures. *Lancet* 1999; **354**: 1071-1077 [PMID: 10509498 DOI: 10.1016/s0140-6736(98)11134-0]

29 **Yapar N**, Hosgor M, Çavuşoğlu C, Ayanoğlu Ö, Ermertcan Ş, Özinal MA. Investigation of infection and colonization in long-term intravenous catheter use. *J Infect* 1998; **12**: 333-336

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SYSTEMATIC REVIEWS

SARS-CoV-2 (COVID-19), viral load and clinical outcomes; lessons learned one year into the pandemic: A systematic review

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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections is diagnosed *via* real time reverse transcriptase polymerase chain reaction (RT-PCR) and reported as a binary assessment of the test being positive or negative. High SARS-CoV-2 viral load is an independent predictor of disease severity and mortality. Quantitative RT-PCR may be useful in predicting the clinical course and prognosis of patients diagnosed with coronavirus disease 2019 (COVID-19).

AIM

To identify whether quantitative SARS-CoV-2 viral load assay correlates with clinical outcome in COVID-19 infections.

METHODS

A systematic literature search was undertaken for a period between December 30, 2019 to December 31, 2020 in PubMed/MEDLINE using combination of terms "COVID-19, SARS-CoV-2, Ct values, Log_{10} copies, quantitative viral load, viral dynamics, kinetics, association with severity, sepsis, mortality and infectiousness''. After screening 990 manuscripts, a total of 60 manuscripts which met the inclusion criteria were identified. Data on age, number of patients, sample sites, RT-PCR targets, disease severity, intensive care unit admission, mortality and conclusions of the studies was extracted, organized and is analyzed.

RESULTS

At present there is no Food and Drug Administration Emergency Use Authorization for quantitative viral load assay in the current pandemic. The intent of this research is to identify whether quantitative SARS-CoV-2 viral load assay correlates with severity of infection and mortality? High SARS-CoV-2 viral load was found to be an independent predictor of disease severity and mortality in majority of studies, and may be useful in COVID-19 infection in susceptible individuals such as elderly, patients with co-existing medical illness such as diabetes, heart diseases and immunosuppressed. High viral load is also associated

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with elevated levels of TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10 and C reactive protein contributing to a hyper-inflammatory state and severe infection. However there is a wide heterogeneity in fluid samples and different phases of the disease and these data should be interpreted with caution and considered only as trends.

CONCLUSION

Our observations support the hypothesis of reporting quantitative RT-PCR in SARS-CoV-2 infection. It may serve as a guiding principle for therapy and infection control policies for current and future pandemics.

Key Words: COVID-19; SARS-CoV-2; Viral load; Severe sepsis; Dynamics; Mortality

Core Tip: High viral load in Coronavirus-2 infections is an independent predictor of disease severity, mortality and prognosis. However there is a wide heterogeneity in fluid samples at different phases of the disease and data should be interpreted with caution. In aggregate, observations support the hypothesis of checking and reporting viral load by quantitative real time reverse transcriptase polymerase chain reaction, instead of binary assessment of a test being positive or negative. Longitudinal analysis with viral loads should be conducted for interpretation of outcome data. This may be the guiding principle for therapy and infection control policies for future pandemics.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and associated mortality continues to rise and spread unabated in United States and worldwide. Coronavirus disease 2019 (COVID-19) infection is diagnosed *via* real time reverse transcriptase polymerase chain reaction (RT-PCR). However this assessment is qualitative and reported as a binary positive or a negative test. There is an urgent need to identify high risk patients early in the course of the illness, which includes rapid testing. Quantitative viral load may provide valuable assessment in risk stratification and may assist with early implementation of therapy in susceptible populations such as elderly, immunosuppressed patients with comorbidities.

Quantitative viral RNA load as determined by qRT-PCR assay and reported as cycle threshold (Ct < 38) value and/or $\log_{10}$ (viral copies/mL) from respiratory or blood specimens is a critical factor in diagnosing SARS-CoV-2 virus infection[1-60]. In addition, viral load dynamics in body fluids such as plasma, serum, urine, feces is emerging as a factor in determination of severe inflammation, infectiousness and transmissibility of COVID-19[1-60].

Similar association of high viral load along with age, comorbidities and elevated mortality were also demonstrated during the previous SARS-CoV, pandemic in Hong Kong in the year 2003 and MERS-CoV pandemic in middle east in 2012[61-64].

At present there is no Food and Drug Administration (FDA) Emergency Use Authorization issued for quantitative viral load assay in the current pandemic[59]. The intent of this research is to identify whether quantitative SARS-CoV-2 viral load assay correlates with clinical outcomes, particularly if there is any correlation with severity of infection and mortality? This a correlation study and does not imply causation. The author qualitatively examined the available data from different manuscripts to find patterns and generate a hypothesis for future research. These may assist clinicians; epidemiologist and health care policy makers develop strategies to improve care in COVID-19 sepsis.

MATERIALS AND METHODS

A systematic literature search was undertaken in PubMed/MEDLINE using combination of terms "COVID-19, SARS-CoV-2, Ct values, Log_{10} copies, quantitative viral load, viral dynamics, kinetics, severity of symptoms, sepsis, mortality'' for a period between December 30, 2019 to December 31, 2020. Review of manuscripts was performed according to principles outlined in Cochrane handbook. Figure 1 (PRISMA flow diagram).

Due to an explosion of COVID-19 related research and manuscripts, search was limited to adult (> 18 years) human subjects and published in English language journals. All data is retrospective, de-identified and conforms to the ethical principles in "Declaration of Helsinki". Manuscripts from preprint non-peer reviewed servers, review articles and individual case reports were excluded. After screening 990 manuscripts, a total of 60 manuscripts which met the inclusion criteria were identified. Data on age, number of patients, sample sites, RT-PCR targets, disease severity, intensive care unit (ICU) admission, mortality and conclusions of the studies was extracted, organized and presented (Table 1). Other relevant articles with relevant information on viral load assessment and mortality, severity and infectiousness and transmission were also included for discussion purposes. During the course of the pandemic in the year 2020, the author followed the PubMed literature on the research question and carefully tracked and evaluated the consistency and quality of the published articles to ensure credibility, reliability, transferability and reduce the risk of bias. The full text of selected articles was fully read, and the key findings were extracted. To establish reliability the author recorded the data in a table and updated assessment of the results. The use of the tables for recording manuscripts provided this researcher with a chance to evaluate the results of the data provided in each manuscript and follow the trends in this topic. The table also helped in construction of concise conclusions of the data. The table is transparent and reproducible and may be useful for other researchers to follow upon.

Due to a high heterogeneity in patient population, data from different countries, different methods in sampling, comorbidities, and different parameters used, the content was analyzed and is summarized using qualitative (descriptive) terms. Data with P value (< 0.05) was considered statistically significant.

RESULTS

Sixty manuscripts met the inclusion criteria with our research question, and are summarized[1-60]. Twenty eight manuscripts (46%) were reported from China[1,2,4-13,15,17,20-22,25,26,29,32,36,38,39,42,43,52,54], Eight (13%) studies from United States [27,28,30,35,40,53,59,60], Four (6%) were from France[3,33,37,56] and South Korea[19,31,34,50], Three (5%) from Spain[48,57,58], Two (3%) were from Italy[18,24] and Germany[14,41] and One manuscript (2%) was from Switzerland[16], Hong Kong[23], Sweden[44], Norway[45], Israel[49], Greece[55], Japan[47], Turkey[46], Brazil[51] (Table 1).

A total of 10514 patients were pooled from all reported studies. Quantitative RT-PCR and viral dynamics are reported in samples obtained from nasopharyngeal and oropharyngeal swabs, saliva, sputum, bronchial/tracheal lavage, feces, plasma/serum and urine samples. All studies had initial COVID-19 diagnosed on upper respiratory samples. Subsequent quantitative viral load was obtained and described from various other specimens and body fluids.

RT-PCR targets of SARS-CoV-2 virus included the following genes: *ORF1* (open reading frame), *N* (Nucleocapsid), *E* (Envelope), *RdRp* (RNA dep RNA polymerase), *5'UTR* (5'untranslated region). Forty-three studies (70%) reported viral kinetics in Ct values and 18 (30%) reported it as Log_{10} copies/mL values.

Association between viral load and disease severity

Thirty-six studies (7222 patients) demonstrated a significant association between pharyngeal viral load at onset of symptoms with severity of COVID -19 and ICU care [4-9,13,15,17-20,24,26,27,29,30,32,33,36-38,41,42,44,45,48,49,51-56,58,59]. The majority of these studies reported highest viral load at onset of symptoms.

Most studies consistently defined severity of illness and sepsis as: Respiratory rate ≥ 30 beats/min, resting-state oxygen saturation ≤ 93%, arterial partial pressure of oxygen/oxygen concentration ≤ 300 mm Hg or mechanical ventilation, shock, or multiple organ failure requiring care in ICU[4,8,29,65].

Table 1 Manuscript evaluating quantitative viral load assay and coronavirus disease 2019 outcomes. Sixty manuscripts meet the inclusion criteria

Ref./country	Number of patients	Age (yr)	Sampled sites	Quantitative viral load reported as Ct values or Log_{10} copies /mL /*RTPCR* gene target	Correlation with severity of sepsis	Correlation with mortality	*P* value	Merits of the study/key points
He *et al*[1], China	94	Median 47 yr	Nasopharynx	Ct values/; N gene	Not reported	Not reported	NR	Highest viral load at pre-symptomatic stage and infectiousness peaks before symptom onset.
Xu *et al*[2], China	51	Median 37 yr	Nasopharynx, BAL, Anal swab	Ct values/; ORF1ab and N gene	No	No	> 0.05	The quantitative viral load and infectiousness may be the similar for primary (imported form epicenter) and secondary and tertiary exposed group of patients but decrease rapidly (in 14 d) in tertiary patients.
Lescure *et al*[3], France	5	Median 46 yr	Nasopharynx, Stool, Plasma	Log_{10}copies/mL; RdRp-IP1 gene, E gene	No	Inadequate sample size	NR	Presymptomatic patients may have a high viral load and be highly infectious.
Liu *et al*[4], China	76	Median 50 yr	Nasopharynx	Ct values; Gene not reported	Yes	No	< 0.005	Patients with severe COVID-19 have a higher mean viral load (60 times higher) and long shedding period.
To *et al*[5], China	23	Median 62 yr	Oropharynx	Log_{10}copies/mL/; RdRp gene	Yes	Not reported	0.56	Peak viral load occurs at onset of symptoms and is correlated with increasing age and severity although not statistically significant.
Shen *et al*[6], China	5	Median 60 yr	Nasopharynx	Ct values; Gene not reported	Yes	No	NR	Patients with severe sepsis and high quantitative viral load benefit from convalescent plasma. The viral load became negative in all 5 patients in 12 d with clinical improvement.
Duan *et al*[7], China	10	Median 52.5 yr	Nasopharynx	Ct values; ORF1ab and N gene	Yes	No	< 0.001	Resolution of severe sepsis and negative viral load with convalescent plasma infusion.
Chen *et al*[8], China	48	Median 63 yr	Oropharynx. serum	Ct values; ORF1ab and N gene	Yes	Yes	< 0.001	Serum viremia and viral load associated with severity and poor prognosis. High RNAaemia is associated with elevated IL-6 levels.
Pan *et al*[9], China	82	Not reported	Oropharynx. Sputum, Stool	Log_{10}copies/mL; N gene	Yes	Yes	NR	Viral load is high on presentation. Stool samples may turn positive later in the disease.
Cao *et al*[10], China	199	Median 58 yr	Oropharynx	Log_{10}copies/mL; N and E gene	Not reported	No	NR	Lopinavir-Ritonavir did not aid with clinical improvement, reduce mortality or reduce the viral loads.
Wang *et al*[11], China	237	Median 65 yr	Oropharynx, Sputum	Log_{10}copies/mL; Gene not reported	Not reported	Not reported	NR	Remdesivir group does not decrease viral load compared to control group, however it may have faster time to clinical improvement.
Zou *et al*[12], China	18	Median 59 yr	Nasopharynx, Oropharynx	Ct values; ORF1b	Not reported	Not reported	NR	High viral load begins in the presymptomatic period and may suggest high infectivity.
Wang *et al*[13], China	23	Median 56 yr	Nasopharynx, Oropharynx, sputum, fecal, urine, plasma	Ct values; RdRp and N gene	Yes	None	< 0.001	High viral load and shedding from multiple tissues occurs for a prolonged period in severe cases. Feces remains positive for a prolonged time.
Wölfel *et al*[14], Germany	9	Not reported	Oropharynx, Sputum, stool, serum, urine	Log_{10}copies/mL; RdRp and E gene	No	No	NR	High viral load begins in the presymptomatic period and may continue beyond 10 d after symptoms ensue suggest high infectivity. No positivity in stool, urine or serum. All cases were with mild symptoms.
Zheng *et al*[15],	96	Median	Nasopharynx,	Ct values and Log_{10}copies/mL;	Yes	Not reported	0.03	High respiratory viral load associated with disease severity and serum

China		55 yr	Oropharynx, sputum, fecal, urine, plasma	ORF1ab				positivity and stool shedding occurs later and persists for a longer period.
Baggio *et al*[16], Swiss	352 adults, 53 children	Mean 36.5 yr	Nasopharynx	Log_{10}copies/mL; ORF1ab and E gene	Not reported	Not reported	NR	Children and adults can have same variation of viral loads, but risk of transmission and lower susceptibility in children may have other contributing factors.
Shi *et al*[17], China	114	Median 43.5yr	Oropharynx, serum	Log_{10}copies/mL; N gene	Yes	Not reported	< 0.001	High viral loads associated with severe sepsis in female patients.
Clementi *et al*[18], Italy	200	Mean 64 yr	Nasopharynx	Ct values; ORF1ab and E gene	Yes	Not reported	0.08	Higher viral loads associated with older age group and severity of sepsis.
Kwon *et al*[19], Korea	31	Mean 50 yr	Nasopharynx	Ct values; RdRp and N gene	Yes	None	0.093	High viral loads correlated with elevated cytokine profile and severity of sepsis.
Yu *et al*[20], China	92	Mean 55 yr	Sputum	Ct values/N and ORF1b	Yes	No	0.017	Higher baseline sputum viral load on admission is associated with severe disease.
Liu *et al*[21], China	31	Median 58 yr	Nasopharynx, sputum	Ct values; ORF1ab and N gene	Not reported	Not reported	NR	Viral load is higher in deep sputum samples and have a higher shedding and transmission capacity.
Zhou *et al*[22], China	31	Median 41 yr	Nasopharynx	Ct values; ORF1ab and N gene	No	No	NR	Asymptomatic patients have high viral loads and continue viral shedding and transmission.
Cheung *et al*[23], Hong Kong	59	Median 58.5 yr	Stool	Log_{10}copies/mL; Gene not reported	No	No	= 0.019	Stool viral loads are higher in patients with diarrhea and may persist after negative respiratory specimens.
Azzi *et al*[24], Italy	25	Mean 61.5 yr	Saliva	Ct values; 5'UTR	Yes	Not reported	= 0.04	High salivary viral loads may be associated with severe disease and may persist after the negative respiratory specimens. High viral load associated with high serum LDH suggestive of tissue damage.
Chen *et al*[25], China	22	Median 36.5 yr	Saliva, feces, Oropharynx	Ct values; ORF1ab and N gene	No	No	NR	Sputum and stool viral load remains positive after pharyngeal samples turn negative. Indicating the infectivity may persist after negative pharyngeal samples.
Huang *et al*[26], China	16	Median 59.5 yr	Nasopharynx, sputum, tracheal aspirates, fecal, urine, plasma	Ct values; N gene	Yes	No	< 0.01	In severe cases higher viral load is demonstrated in deep sputum and tracheal aspirates compared to upper respiratory tract specimens.
Pujadas *et al*[27], United States	1145	Mean 64.6 yr	Nasopharynx	Log_{10}copies/mL; RdRp and N gene	Yes	Yes	= 0.003	High viral load is an independent predictor of mortality.
Arons *et al*[28], United States	57	Mean 75 yr	Nasopharynx, Oropharynx	Ct values; N1 and N2	No	Not reported	NR	High viral loads demonstrated in presymptomatic, asymptomatic cases, favoring high transmissibility in close knit nursing home population.
Huang *et al*[29], China	308	Median 63 yr	Nasopharynx, Oropharynx	Ct values; ORF1ab	Yes	Yes	< 0.001	High viral load associated with critical disease and mortality. Sputum samples have higher viral loads.
Magleby *et al*[30], United States	678	Median 69 yr	Nasopharynx,	Ct values; ORF1b and E gene	Yes	Yes	< 0.001	High viral load is an independent risk factor for severe sepsis, intubation and death.
Park *et al*[31], Korea	46	Median 26 yr	Nasopharynx, Oropharynx, sputum ,	Ct values; RdRp, N and E gene	No	No	NR	High fecal viral load and shedding, follows and persists after respiratory symptoms resolve for up to 50 d.

			Stool					
Yu *et al*[32], China	76	Median 40 yr	Nasopharynx, Oropharynx, sputum, urine, plasma	Ct values; ORF1b and N gene	Yes	None	< 0.001	Digital droplet PCR is superior for patients with high suspicion but negative RTPCR. High viral load correlated with risk for progression and disease activity.
Blot *et al*[33], France	14	Median 67 yr	Broncho-alveolar fluid	Log_{10}copies/mL; RdRp	Yes	Not reported	= 0.013	Higher viral load associated with worse sepsis related organ failure (SOFA) scores.
Kim *et al*[34], Korea	13	Median 30 yr	Nasopharynx	Ct values; RdRp and E gene	No	No	NR	Patient with mild or asymptomatic infections are infectious before symptoms appear and 14 d of isolation may be sufficient in asymptomatic carriers.
Argyropoulos *et al*[35], United States	205	Median 60 yr	Nasopharynx	Log_{10}copies/mL; RdRp and N gene	Decreased	Decreased	< 0.001	Study shows inverse correlation of high viral load with duration, severity of sepsis and no correlation with survival.
Xu *et al*[36], China	85	Median 56 yr	Nasopharynx, Oropharynx, serum	Ct values; ORF1b and N gene	Yes	Yes	< 0.001	Detection of high serum viral load in the serum increases the severity of organ damage, sepsis and mortality.
Veyer *et al*[37], France	58	Median 55.1 yr	Plasma	Log_{10}copies/mL; ORF1b and N gene	Yes	Yes	= 0.036	Detection of high Viral load in the serum increases the severity of sepsis and mortality.
Lin *et al*[38], China	217	Median 50 yr	Nasopharynx, Oropharynx, anal	Ct values; ORF1b and N gene	Yes	No	= 0.006	Anal viral load remains positive longer and is correlated with severity of sepsis and ICU admission.
Wang *et al*[39], China	275	Median 49 yr	Oropharynx	Ct values; ORF1b and N gene	No	No	= 0.824	Similar viral loads between severe and mild cases, no correlation of viral load to ICU admission, severity or mortality.
Kimball *et al*[40], United States	23	Mean 80.7 yr	Nasopharynx, Oropharynx	Ct values; N1, N2 genes	No	No	= 0.3	High viral loads in unrecognized asymptomatic and presymptomatic patients may contribute to infectiousness and transmission.
Schwierzeck *et al*[41] ,Germany	12	Not reported	Nasopharynx	Ct values; E and RdRp genes	Yes	No	= 0.007	High viral load, 200 times greater in symptomatic patients compared to asymptomatic patients.
Xia *et al*[42], China	10	Mean 56.5 yr	Nasopharynx	Ct values; ORF1ab and N gene	Yes	No	NR	Higher viral load associated with severe symptoms and increased neutrophil/lymphocyte ratio.
Huang *et al*[43], China	41	Median 49 yr	Nasopharynx, Oropharynx, sputum, BAL	Ct values; 5'UTR	No	No	No	Patients with high viral load with RNAeamia had severe infection, elevated cytokine levels, and mortality but not statistically significant.
Hagman *et al*[44], Sweden	167	Median 63	Nasopharynx, Oropharynx, sputum, Blood	Ct values; E, RdRp, ORF1 genes	Yes	Yes	P < 0.05	Viral RNAemia on admission was associated with eight fold increased risk of in hospital death.
Prebensen *et al*[45], Norway	123	Median 64	Nasopharynx, Oropharynx, sputum, Blood	Ct values for respiratory specimens; Log_{10}copies/mL for plasma samples; E gene	Yes	Yes	< 0.001	Higher viral loads associated with ICU admission and death.
Hasanoglu *et al*[46], Turkey	60	Mean 32	Nasopharynx, Oropharynx, sputum, urine, Blood, rectal	Ct values; RdRp gene	Decreased	Decreased	= 0.0141	Viral loads in younger asymptomatic patients were significantly higher compared to elderly, symptomatic patients.
Kawasuji *et al*[47], Japan	28	Median 45	Nasopharynx	Log_{10}copies/mL; N gene	No	No	= 0.015	High admission nasopharyngeal viral load associated with increased risk of transmission.

Bermejo-Martin *et al*[48], Spain	250	Median 66	Nasopharynx, Oropharynx, sputum, urine, Blood, rectal	Log_{10}copies/mL; N gene	Yes	Yes	< 0.001	Increased serum viral load associated with increased severity, mortality and dysregulated host response.
Shlomai *et al*[49], Israel	170	Median 62	Nasopharynx	Ct values; N gene	Yes	Yes	< 0.0001	Increased hypoxemia, severity and eight fold increase in mortality.
Ra *et al*[50], Korea	213	Median 25	Nasopharynx	CT value; E, N, RdRp gene	No	No	None	Comparable viral load in asymptomatic and symptomatic patients, asymptomatic patients contribute to ongoing transmission.
Faico-Filho *et al*[51], Brazil	875	Median 48	Nasopharynx	Ct value; N gene	Yes	Yes	< 0.0001	Admission nasopharyngeal viral load was independently associated with increased mortality.
Chen *et al*[52], China	52	Median 62	Blood, oropharynx	Log_{10}copies/mL; ORF1ab	Yes	Yes	< 0.001	Increased RNAemia associated with severity, markers of inflammation and mortality.
Fajnzylber *et al*[53], United States	88	Median 57	Nasopharynx, Oropharynx, sputum, Blood	Log_{10}copies/mL; N gene	Yes	Yes	= 0.009	Increased viremia associated with severity, progression and mortality.
Zhou *et al*[54], China	195	Median 66	Oropharynx	Ct value; N gene, ORF1ab	Yes	Yes	< 0.005	High viral load associated with multi organ failure and death.
Maltezou *et al*[55], Greece	1122	Mean 46	Nasopharynx, Oropharynx	CT value; E, RdRp gene	Yes	Yes	< 0.05	High viral load correlated with intubation and in hospital mortality.
Bitker *et al*[56], France	129	Median 69	Nasopharynx, Oropharynx, sputum	Ct value; ORF1ab	Yes	Yes	< 0.05	High viral load associated with increased mortality.
Carrasquer *et al*[57], Spain	169	Median 67	Nasopharynx	Ct value; E, N gene, ORF1ab	No	No	= 0.029	High viral load statistically not associated with in hospital mortality.
de la Calle *et al*[58], Spain	455	Mean 64	Nasopharynx	Ct value; N gene	Yes	Yes	= 0.022	High viral load associated with respiratory failure, and 30 d mortality.
Bryan *et al*[59], United States	109	Mean 65	Nasopharynx	Ct value; N gene	Yes	Yes	= 0.01	The high nasopharyngeal viral load on admission was independently associated with greater mortality.
Choudhuri *et al*[60], United States	1044	Mean 65	Nasopharynx	Ct value; ORF1ab	No	Yes	< 0.001	High viral load is an independent predictor of increased mortality.

Data on country of origin, age, number of patients, sample sites, real time reverse transcriptase polymerase chain reaction targets, correlation with sepsis and mortality and key conclusions. NR: Not reported; ORF: Open reading frame; E: Envelope; N: Nucleocapsid; 5'UTR: 5 prime untranslated; RdRp: RNA dependent RNA polymerase; Ct: Cycle threshold; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; COVID-19: Coronavirus disease 2019.

There is variation observed in kinetics, tissue distribution and antibody response between mild and severe infections. Wang *et al*[13] analyzed a cohort of 12 severe and 11 mildly ill patients and demonstrated a significant difference in the initial nasopharyngeal peak viral load ($P < 0.001$) between two groups. Subsequent prolonged viral shedding in other body fluids and stool occurred with detectable viral load for up to 40 d (days) in severely ill compared to 15 d in mildly ill group. Viral RNA was detected from respiratory tract, stool, plasma and urine samples in the

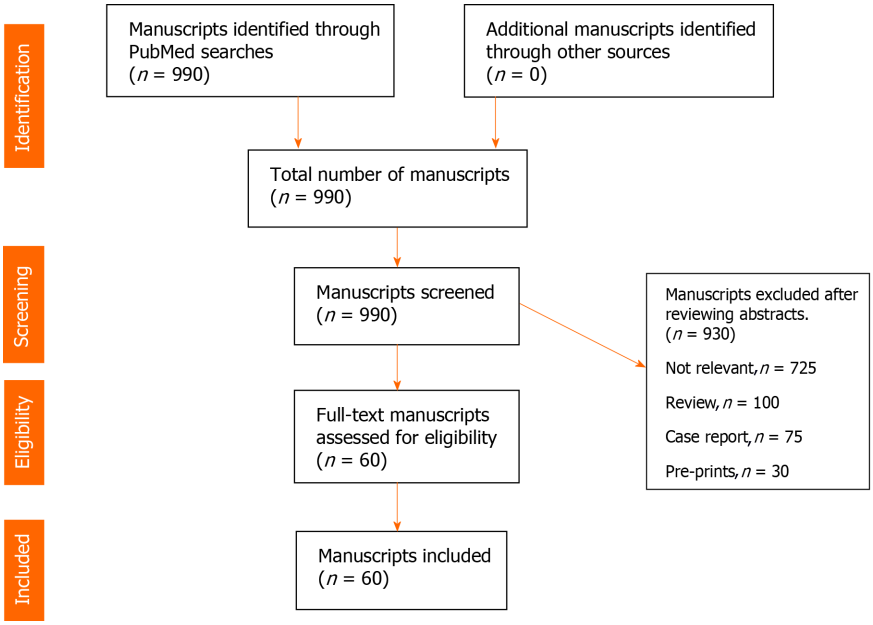

Figure 1 PRISMA flow diagram.

severe group. Mildly ill patients had viral shedding restricted to respiratory tract and no virus was detected 10 d after onset of symptoms[13].

Yu *et al*[20] analyzed their cohort of 92 patients and observed that high viral load in baseline sputum samples was linearly associated with severity and risk of disease progression ($P < 0.017$).

Another cohort of 96 patients with mild and severe infections demonstrated similar viral kinetics. Respiratory viral load remained elevated in the severe group up to the third and fourth week after disease onset, compared to milder group where viral load peaked in the second week followed by a decline. Subsequent viral detection in serum samples was also higher in patients with severe disease than in patients with mild disease (45% *vs* 27%, $P < 0.03$)[15].

In general nasopharyngeal viral levels remained high in severe group and, begin to decrease after 14 d of symptom onset[4,15,65]. Subsequently, samples from other sites may also test positive for the virus. For example, viral load from stool samples were found to peak during the third and fourth weeks after disease onset and continue to remain positive during convalescence[9,13,15,19,25,31]. Some studies also reported presence of high viral load in stool up to 50 d after onset of COVID-19 symptoms[31, 38].

Significance of viral load in stool remains unclear, whether it represents a true infection or residual viral nucleic acid and not transmissible live virus. Gastrointestinal epithelium also expresses angiotensin-converting enzyme II (ACE-2) receptors. Infection of gastrointestinal (GI) tract may occur primarily from swallowed nasopharyngeal secretions or due to dissemination to GI tract from viremia[23]. Eighteen studies (5479 patients) demonstrated a statistically significant (P value < 0.005) association between higher viral load in different samples and severity of disease[4,7,8,13,17,27,29,30,32,36,45,48,49,51,52,54-56].

Liu *et al*[4] analyzed their cohort of 46 mild and 30 severely ill patients with elevated nasopharyngeal viral load and demonstrated an association with severity. Viral load was 60 times higher in severe cases and with severe clinical outcomes ($P < 0.005$). Mild cases had viral clearance, with 90% of patients testing negative after 10 d. In contrast, all severe cases had persistently elevated viral load beyond 10 d of symptoms were elderly and required ICU care.

In a cohort of patients on dialysis, Schwierzeck *et al*[41] also demonstrated a similar association with severity. Ct values of symptomatic cases were significantly lower compared to asymptomatic cases (22.55, 29.94, respectively, $P = 0.007$), indicating approximately 200-fold higher viral load[41]. Similarly other authors from their cohorts from different countries Bermejo-Martin *et al*[48]; Spain, Shlomai *et al*[49]; Israel, Chen *et al*[52]; China, Zhou *et al*[54]; China, Maltezou *et al*[55]; Greece have demonstrated a statistically significant association between admission high viral load and intubation, ICU care and multi-organ dysfunction.

Collectively these data from different cohort of patients suggests that severe COVID-19 patients with a high viral load correlate with higher risk for severe infection with ICU admission and multi-organ dysfunction. Factors common to these cohorts was increased age, and active preexisting medical co-morbidities.

Association between viral load and inflammatory markers

Higher viral load on admission samples were also associated with elevated levels of IL-6, cytokines, lactate dehydrogenase (LDH), lymphopenia and elevated neutrophil/lymphocyte ratio; indicative of poor sequential organ failure assessment (SOFA) scores and associated with hyper-inflammatory state contributing to the severity of sepsis[8,19,24,29,33,36,37,42,48,49,52,65,66].

In a cohort of 48 patients, Chen *et al*[8] reported an association between high viral load in serum with elevated Il-6 Levels (≥ 100 pg/mL) and cytokine storm in critical compared to mildly ill patients ($P < 0.001$). These patients had a higher incidence of multi-organ failure and mortality.

Similarly Xia *et al*[42] in their cohort of 10 patients with severe illness and elevated nasopharyngeal viral load reported severe lymphopenia with CD4+ lymphocyte counts as low as 61 cells/uL (reference value: 355-1213 cells/μL). Neutrophil to lymphocyte ratio was also elevated in this group.

Liu *et al*[65] reported their cohort of 46 patients with severe illness and elevated nasopharyngeal viral load. $CD4^+$ and $CD8^+$T lymphocyte count displayed a linear negative correlation ($P < 0.001$) with high viral count; and positively correlated with IL-2R, prothrombin time, lactate dehydrogenase, and hypersensitive troponin T ($P = 0.002$, $P = 0.009$, and $P < 0.001$, respectively). Also elevated, were levels of inflammatory factors, IL-2R, IL-6, IL-8 Levels in the severe compared to mild group ($P = 0.022$, 0.026, and 0.012, respectively)[65].

Blot *et al*[33] in their series of 14 patients demonstrated a positive correlation of high nasopharyngeal viral load on admission with risk of hypoxemia, increased oxygen requirements and SOFA score in respiratory distress syndrome patients ($P = 0.013$). Similar association with increase in severity of sepsis, organ damage and mortality was also reported by Xu *et al*[36].

Lucas *et al*[66] in their series of 113 patients with COVID-19 patients demonstrated an overall increase in cells of innate lineage and a reduction in T lymphocytic cell counts. High viral load correlated significantly with levels of IFNα, IFNγ, TNF and tumor necrosis factor-related apoptosis-inducing ligand. Chemokines responsible for monocyte recruitment correlated significantly with viral load in severe disease. Inflammasome associated cytokines were also elevated, including IL-1α, IL-1β, IL-6, IL-18 and TNF[66].

Similarly Han *et al*[67] in their series of 60 critical patients demonstrated high levels of cytokines TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10 and C reactive protein (CRP). Serum IL-6 and IL-10 Levels were significantly higher in critically ill compared to moderately ill group. The levels of IL-10 positively correlated with CRP ($r = 0.41$, $P < 0.01$)[67].

Collectively these studies provide evidence that high viral load may be a surrogate marker for predicting inflammation and severity in COVID-19 infection.

Association between viral load and mortality

Subgroup analysis of 20 studies (7183 patients) demonstrated an association of admission viral load with in hospital mortality[8,9,27,29,30,36,37,45,46,48,49,51-56,58-60]. Majority of patients in this category were older (median > 65 years) and with medical comorbidities[8,9,29,30,33,36,37,45,46,48,49,58-60]. High admission viral load was an independent risk factor for in hospital mortality ($P < 0.005$)[8,27,29,30,36,46,48,49,51,52,54,59,60].

Pujadas *et al*[27] demonstrated an association of viral load as an independent predictor of mortality in a cohort of 1145 hospitalized patients. Mean $\log_{10}$ viral loads significantly differed between patients who survived [$n = 807$; mean $\log_{10}$ viral load 5.2 copies/mL (SD 3)] *vs* those who succumbed [$n = 338$; 6.4 copies/mL (SD2.7)]. Cox proportional hazards model was adjusted for age, sex, asthma, atrial fibrillation, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, heart failure, hypertension, stroke, and race. The results demonstrate a significant independent association between viral load and mortality [hazard ratio 1.07 [95% confidence interval (CI): 1.03–1.11), $P = 0.0014$], and 7% increase in hazard for each log transformed copy/mL. Univariate survival analysis also demonstrated a significant difference in survival probability between high and with low viral load ($P = 0.0003$), with a mean follow-up of 13 d and a maximum follow-up of 67 d[27].

Magleby *et al*[30] in their cohort of 678 patients demonstrated that higher viral load was associated with increased age, comorbidities, smoking status, and recent chemotherapy. Mortality was highest, 35.0% in the high viral (Ct < 25; n = 220) followed by 17.6% in the medium viral (Ct 25-30; n = 216) and 6.2% with a low viral load (Ct > 30; n = 242; P < 0.001). The need for mechanical ventilation was also highest in the high viral (29.1%), compared to medium (20.8%) and low viral load (14.9%; P < 0.001) group. High viral load was independently associated with mortality [adjusted odds ratio (OR) 6.05; 95%CI: 2.92-12.52; P < 0.001] and intubation (adjusted OR 2.73; 95%CI: 1.68-4.44; P < 0.001) in multivariate models.

Similarly Huang *et al*[29] in their analysis of 308 patients demonstrated a high viral load associated with in-hospital mortality in (6/16) of critical patients, while no mortality was observed in the low viral load group (P < 0.0001). High viral load was associated with myocardial damage, elevated troponins, coagulopathy, abnormal liver and renal functions. Elevated IL-6, LDH, and elevated neutrophil counts and reduced CD4+, CD8+ lymphocytes were noted in deceased patients P < 0.0001)[29].

In a cohort of 109 patients Bryan *et al*[59] demonstrated high viral load on admission was associated with a significantly increased 30-d mortality (OR, 4.20; 95%CI, 1.62–10.86. Their data suggested that a CT value of 22 may serve as a useful discrete cutoff for significant viral replication that is associated with mortality[59].

In a cohort of 1044 patients, Choudhuri *et al*[60] demonstrated a statistical correlation of Ct value at admission was higher for survivors (28.6, SD = 5.8) compared to non-survivors (24.8, SD = 6.0, P < 0.001). After adjusting for age, gender, body mass index, hypertension and diabetes, increased cycle threshold was associated with decreased odds of in-hospital mortality (0.91, CI: 0.89-0.94, P < 0.001)[60].

Collectively these multiple cohort of patients from different studies shows a trend of the association of high viral load and mortality in hospitalized patients.

Association between viral load and infectivity, transmission and antibodies to SARS-CoV-2

Although not statistically significant, 20 studies (1857 patients) indicated the importance of high viral load dynamics with infectiousness and transmissibility (P > 0.05-0.53)[1-3,10-12,14,16,21,22,23,25,28,31,34,39,40,43,47,50].

Association between viral load and infectivity remains unclear, but earlier peak in viral load in SARS-CoV-2 infection suggests that infectivity may be higher earlier in the course than would be expected based on the SARS model[5,62,63].

Subgroup analysis suggests these patients are younger and had milder disease and may be highly infectious and transmit virus to the population given their asymptomatic or presymptomatic nature of illness. These studies shed light on high viral load and its association with infectivity and transmissibility. Highest respiratory viral load was noted at pre-symptomatic stage and infectiousness peaked before symptom onset [1,2,3,5,12,14,16,22,34,40,47,50].

He *et al*[1] demonstrated an infectiousness profile on 77 infector–infected transmission pairs. Highest viral load in oropharynx at the time of symptom onset correlated with infectiousness. Presymptomatic transmission was 44% (95%CI, 30%–57%) whereas infectiousness started at 12.3 d (95%CI, 5.9-17 d) before symptom onset and peaked at onset (95%CI: –0.9 to 0.9 d). They estimated that proportion of presymptomatic transmission was 37%-48%[1].

Xu *et al*[2] reported on 51 symptomatic patients, demonstrating transmission from primary (patients who visited the epicenter, Wuhan), to secondary (patients who came into contact with primary) and tertiary (patients who came into contact with only secondary cases). Their findings suggested incubation period in tertiary group was longer compared to primary and secondary groups (both P < 0.05). Ct values detected in tertiary were similar to those for the imported and secondary patients at the time of admission (both P > 0.05). For tertiary group, the viral load was undetectable in half of patients (52.63%) on day 7 and in all patients on day 14. One third of patients in imported and secondary groups remained positive on day 14 after admission. They concluded that infectivity of SARS-CoV-2 may gradually decrease in tertiary patients [2]. This study emphasizes that early quarantine and lock down measures may have mitigated the spread of disease in countries that enforced it strictly. The reason for decrease in infectivity from secondary to tertiary exposed patient remains unclear. Although speculative, this may be due to reduced quantitative viral load transmitted and other strict mask and quarantine measures[2,44].

Some reports demonstrated an association of high viral load and risk of transmission in a closed knit population[28,40]. In a cohort of 80 patients including both health care workers and nursing home residents from COVID-19 outbreak in Washington State, high viral load in unrecognized asymptomatic and presymptomatic

patients contributed to infectiousness and transmission. Although the mortality was high in these patients, it did not correlate statistically with the viral load[28]. Similarly Kimball *et al*[40] analyzed their cohort of 23 patients from a long term care facility. Ten (43%) had symptoms on testing, and 13 (57%) were asymptomatic. Seven days after testing, 10 of these 13 previously asymptomatic residents had developed symptoms and were inferred as presymptomatic at time of testing. The Ct values indicated large quantities of viral RNA in asymptomatic, presymptomatic, and symptomatic residents, suggesting potential for transmission regardless of symptoms[40].

There are at present limits to our understanding and evidence in determining infectiousness and the risk of transmissibility. As described earlier, there is evidence of ongoing viral shedding in various body fluids after symptom resolution in COVID infection and may be prolonged, especially in stool samples compared to respiratory secretions (P < 0.001-0.5)[9,13,15,19,25,31,38,67]. Currently there is no reported evidence of fecal –oral transmission. Further the severity of illness also appears to extend the duration of viral shedding. However, based on current data, there is no convincing evidence that duration of shedding correlates with duration of infectivity. The viral nucleic acid detected in various body fluids later in the course of infection may represent non-viable fragments of virions.

Wölfel *et al*[14] demonstrated that live virus can be cultured from respiratory samples in patients with positive SARS-CoV-2 RT-PCR. However, the percentage of positive cultures declined and no live virus was successfully isolated after day 8 from symptom onset despite ongoing high quantitative viral load. Additionally, virus could not be isolated from samples less than 10^5 copies/mL. However a caveat with this cohort was that patients had mild symptoms and were young and middle aged adults. This emphasizes the point that elevated high viral load in convalescing patients may be suggestive but not a definitive factor in infectiousness and transmissibility[14].

There is evidence that children are susceptible to SARS-CoV-2 infection, but frequently do not have symptoms, raising possibility that children could be facilitators of viral transmission. Reports comparing viral kinetics in adults and pediatric patients have demonstrated that children, adolescents and adults can have same variation of viral load, but higher risk of transmission and asymptomatic illness in children may have other contributing factors[16,47,50].

The immune responses of the host to COVID-19 and its relation to infectivity and transmission remain unclear and data is emerging[5,13,59,68,69]. Most patients seroconvert by day 15 after symptom onset and Anti-SARS-CoV-2-NP or anti-SARS-CoV-2-RBD IgG levels correlate with virus neutralization[5]. While risk of transmission after symptom resolution and the presence of antibodies may be lower, it cannot be ruled out with available evidence[1-3,5]. Transmission by asymptomatic or minimally symptomatic individuals also appears likely and highlights the importance of contact tracing and isolation of exposed individuals, especially as transmission potential may be maximal early in course of infection as depicted in the nursing home cohort[28,40]. In their large series of 100 patients Li *et al*[68] demonstrated specific anti SARS-CoV-2 (IgM, IgG, IgA) antibodies to S-1, N, and RBD viral proteins in the serum within two weeks after onset and reached a peak in 17 d and maintained high levels up to 50 d post infection.

Fourati *et al*[69] demonstrated an inverse relationship of lower serum titer of neutralizing antibodies (anti-S1 Ig A and Ig G) with elevated nasopharyngeal viral load and severe COVID-19 sepsis. This may indicate an inability to clear infection and have a deleterious impact on survival. Patients who were alive at 28 d displayed higher titers of anti-S1 Ig A and Ig G on admission compared to those who succumbed [69]. Similar observation was demonstrated by Bryan *et al*[59]; this study demonstrated that detection of anti-SARS-CoV-2 nucleocapsid IgG is associated with lower viral loads in patients. They concluded that high viral loads almost never coexist with SARS-CoV-2 sera-positivity and suggest that persons with anti-SARS-CoV-2 antibodies on admission have reduced 30-d all-cause mortality[59]. Both these studies may suggest that presence of antibody titers on admission, coupled with molecular testing, may be particularly prognostic factor, helpful to assess the disease course for high risk patients who cannot provide a clinical history[59,69]. The mechanism may be due to lower host humoral immune response in the elderly patients with comorbidities.

The heterogeneity of the non-respiratory specimen's limits its significance in explaining the risk of transmission and no correlation can be inferred. Further research is needed. In addition it is also important to determine viability of virus outside the respiratory and gastrointestinal tract at different stages of infection in both asymptomatic and symptomatic individuals. This will improve understanding of transmission risk and allow greater certainty around guidelines for appropriate

contact tracing and quarantine periods[70].

DISCUSSION

SARS-CoV-2 is diagnosed based on nucleic acid test, detecting viral RNA. We briefly discuss the relevance of diagnostics in the context of our research question. Laboratories have set up their RT-PCR techniques with primers and probes and protocols, algorithms following guidelines from United States FDA and Center for Disease Control and Prevention (CDC) and World Health Organization[71]. A reference, limit of detection range is set by each laboratory based on reaction system and amplification conditions, specified according to manufacturer's specifications[72]. These tests are high throughput and have high sensitivities and specificity. Bisoffi *et al* [73] demonstrated that nucleic acid tests have highest performance with 91.8% sensitivity, 100% specificity, 100% PPV (positive predictive value) and 97.4% negative predictive value). Some variation may exist in considering single gene targets. *S* and *RdRp* genes had highest sensitivity (94.1%) at their institution[73]. Factors that may affect sensitivity of tests are duration of illness, site of specimen collection, and viral load. Some authors have reported that false negative rates may occur in up to 30% tests[71]. However, at present there is no clear advantage of choosing one particular gene over another as long as the sample acquisition, preparation and device operations are performed by trained personnel and laboratories[70,71].

Viral load is the quantity of viral RNA in a given volume expressed as infectious particles per milliliter. This is also expressed as Log_{10} copies /mL or Ct value. Ct value represents the number of amplification cycles needed for a target gene to exceed a threshold detection level. It is inversely related to viral load; lower the value of Ct, higher the viral load[3,5,12,70,71]. For SARS-CoV-2 the test results are considered positive when multiple genes had a Ct value less than 38. If only one of target gene had a Ct value of < 38, it is reported as a single test positive[32]. Fung *et al*[74] compared the limit of detection for various assays and reported it to be between 85-499 copies/mL for CDC assays and 74 copies/mL with other commercial high-throughput laboratory analyzers. Digital droplet PCR is another technique useful in situations with a high suspicion of infection but a low viral load or a negative test. This test has an advantage of absolute quantification and higher sensitivity in viral RNA detection especially in low viral load samples[32,75].

Strengths and limitations of this manuscript

This study is a large pooled, qualitative content analysis of 60 manuscripts with a cohort of 10514 patients' from different cohorts and countries evaluating patterns of quantitative viral load in predicting disease severity, mortality, risk of infectiousness, transmissibility, and prognosis in patients with COVID-19. The author presents the relative merits and discusses the objective data presented in these studies. This a correlation study and does not imply causation.

However, there are certain limitations in this study. Since there is a high heterogeneity of samples and data in the majority of these manuscripts, the content analysis is qualitative (narrative) and these data should be interpreted with caution and considered only as trends. Differences in distribution of age, sex, definition of disease severity, and other confounding variables such as medical comorbidities, different virologic tests and heterogeneous samples may contribute to different clinical outcomes. For instance very few studies adjusted their statistic models for the other medical morbidities which could have increased the risk for morbidity and mortality [4,6,7,15,19,27,30]. The majority of these studies are on hospitalized patients which has a potential bias of analyzing the more severely ill amongst the overall infected population. Further variations of ACE 2 receptors and expression in various tissues in different ethnic populations may play a role in virulence and transmissibility of this virus[76]. A viral nucleic acid load from a particular sample assay may not represent an exact systemic viral load in the body; further viral load may also not represent viable virions and may be falsely misleading. In addition there is no consistent trajectory of why certain samples test positive with high virus loads and others do not. Another important point to consider is that, majority of studies is from one country: China and from a few medical centers around the epicenter of outbreak, possibly leading to overlapping of population data in reported manuscripts. Other limiting factors may include the testing protocol and standards, set for RT-PCR targets vary between different laboratories[68-70]. Finally there is always a possibility of observer (author bias) which is to be considered.

Although majority of studies showed a positive association between a high viral load and mortality there were three studies with (434 patients) suggestive of an inverse correlation between the two. Argyropoulos *et al*[35] in their report on 205 patients demonstrated an inverse correlation of admission nasopharyngeal viral load with duration, severity of sepsis and no correlation with survival ($P < 0.001$). The reason for low mortality in this study is unclear. One possible explanation could be due to the fact that viral loads detected from nasopharyngeal samples were obtained at a later time point in the disease course. As we have described earlier, that SARS-CoV-2 viral load peaks earlier in the infection followed by cytokine storm and hyper-inflammation when the innate immune system is unable to control the initial viral replication [61]. At these later times points the viral replication may start to defervesce but the multi-organ dysfunction is secondary to systemic hyper-inflammatory response. Similarly Hasanoglu *et al*[46] on their cohort of 60 patients demonstrated an inverse relationship of high viral load with mortality; however their study had a mean age of 32 signifying a younger age group, where mortality is lower compared to older patients. Another group of 169 patients, reported from Spain by Carrasquer *et al*[57] demonstrated no statistical association of high viral load with in hospital mortality when adjusted to age, gender and serum cardiac troponin levels. The conclusions from this study suggested myocardial damage with medical comorbidities as the cause for increased mortality in susceptible population and not high viral loads.

Why is quantitative viral assay important?

Although infection and inflammation begins with the respiratory tract, it also involves extra pulmonary organs[77]. Isolation of viral nucleic acid in multiple tissues, blood and body secretions are indicative of systemic spread and are indicative of severe infection. Evidence from these manuscripts suggests that high viral load occurs in respiratory tract samples during presymptomatic period and peaks at the onset of symptoms and gradually declines over the next one to three weeks[1,2,3,5,9,12,14,16,22,34,40]. Increased viral load in respiratory tract represents active viral replication and a surrogate marker for predicting severity[28,32,37,61]. This is in contrast to previous SARS-CoV epidemic in 2003 where the peak viral load occurred during second week after symptoms appeared and was positively correlated with increased mortality[5,62,63]. This fact explains the increased infectivity and rapid transmission of SARS-CoV-2 compared to previous SARS-CoV epidemic[5]. Along with comorbidities, assessment of viral load from nasopharynx or sputum may determine the risk of severity of sepsis in symptomatic, hospitalized elderly patients[4,5,18]. High viral load is also associated with elevated cytokine, lymphopenia *i.e.,* markers for inflammation and portends poor prognosis[8,24,33,36,37,42,52,65,66]. Early determination of viral load also has therapeutic benefits, such as administration of convalescent plasma, neutralizing antibodies, antiviral medicines and corticosteroids in susceptible elderly patients[6,7,11].

SARS-CoV-2 pandemic continues to spread unabated in United States and worldwide. This is particularly evident after the end of lock down and social distancing measures with increased mobility of the population. A report from a reference laboratory evaluated 29713 de-identified samples from respiratory tract. 14.9% of samples tested positive. Highest positivity rate was identified in males born between1964-1974. Patients between ages of 11-25 had highest viral load (> 10 Log_{10} copies/mL). The clinical symptoms or outcomes of these patients were not known. This study demonstrates that high viral load in younger group may be an important risk factor for infectivity and transmission in a community, regardless of their symptom status[78].

COVID -19 infections in younger asymptomatic patients, with high viral load may fare well due to their robust physiologic reserve. However, they are at highest risk for transmitting the disease and are called super spreaders. These infections generally appear asymptomatic or milder in younger population, but elderly patients bear the brunt of severe infection, hospitalization and mortality[61,62].

CONCLUSION

High SARS-CoV-2 viral load was found to be an independent predictor of disease severity and mortality in high proportion of studies, and may be useful in predicting the clinical course and prognosis of patients with COVID-19. However there is a wide heterogeneity in fluid samples and different phases of the disease and these data should be interpreted with caution and only considered as trends. In aggregate, these

observations support the hypothesis of checking and reporting viral load by quantitative RT-PCR, instead of binary assessment of a test being positive or negative.

ARTICLE HIGHLIGHTS

Research background

High viral load has an implication in the clinical outcomes in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. At present there is no Food and Drug Administration Emergency Use Authorization for quantitative viral load assay in the current pandemic. Currently the coronavirus disease 2019 (COVID-19) tests are reported as a binary assessment of either positive or negative test.

Research motivation

The intent of this research is to identify whether quantitative SARS-CoV-2 viral load assay correlates with severity of infection and mortality?

Research objectives

To assess high viral load and its association with the severity, mortality, infectiousness in COVID-19 infections.

Research methods

A systematic literature search was undertaken for a period between December 30, 2019 to December 31, 2020 in PubMed/MEDLINE using combination of terms "COVID-19, SARS-CoV-2, Ct values, Log_{10} copies, quantitative viral load, viral dynamics, kinetics, association with severity, sepsis, mortality and infectiousness''. Data on age, number of patients, sample sites, real time reverse transcriptase polymerase chain reaction (RT-PCR) targets, disease severity, intensive care unit admission, mortality and conclusions of the studies was extracted, organized and is analyzed.

Research results

High SARS-CoV-2 viral load was found to be an independent predictor of disease severity and mortality in high proportion of studies, and may be useful in predicting the clinical course and prognosis of patients with COVID-19.

Research conclusions

There is a wide heterogeneity in fluid samples and different phases of the disease and these data should be interpreted with caution and only considered as trends. In aggregate, these observations support the hypothesis of checking and reporting viral load by quantitative RT-PCR, instead of binary assessment of a test being positive or negative.

Research perspectives

In future, longitudinal studies with viral load should be monitored and analyzed, so it can be considered in interpretation of outcome data. It may also be a guiding principle for therapy and infection control policies for current and future pandemics.

REFERENCES

1 **He X**, Lau EHY, Wu P, Deng X, Wang J, Hao X, Lau YC, Wong JY, Guan Y, Tan X, Mo X, Chen Y, Liao B, Chen W, Hu F, Zhang Q, Zhong M, Wu Y, Zhao L, Zhang F, Cowling BJ, Li F, Leung GM. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020; **26**: 672-675 [PMID: 32296168 DOI: 10.1038/s41591-020-0869-5]

2 **Xu T**, Chen C, Zhu Z, Cui M, Dai H, Xue Y. Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19. *Int J Infect Dis* 2020; **94**: 68-71 [PMID: 32179140 DOI: 10.1016/j.ijid.2020.03.022]

3 **Lescure FX**, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, Gaymard A, Bouscambert-Duchamp M, Donati F, Le Hingrat Q, Enouf V, Houhou-Fidouh N, Valette M, Mailles A, Lucet JC, Mentre F, Duval X, Descamps D, Malvy D, Timsit JF, Lina B, van-der-Werf S, Yazdanpanah Y. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis* 2020; **20**: 697-706 [PMID: 32224310 DOI: 10.1016/S1473-3099(20)30200-0]

4 **Liu Y**, Yan LM, Wan L, Xiang TX, Le A, Liu JM, Peiris M, Poon LLM, Zhang W. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis* 2020; **20**: 656-657 [PMID: 32199493 DOI:

10.1016/S1473-3099(20)30232-2]

5 **To KK**, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, Yip CC, Cai JP, Chan JM, Chik TS, Lau DP, Choi CY, Chen LL, Chan WM, Chan KH, Ip JD, Ng AC, Poon RW, Luo CT, Cheng VC, Chan JF, Hung IF, Chen Z, Chen H, Yuen KY. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020; **20**: 565-574 [PMID: 32213337 DOI: 10.1016/S1473-3099(20)30196-1]

6 **Shen C**, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020; **323**: 1582-1589 [PMID: 32219428 DOI: 10.1001/jama.2020.4783]

7 **Duan K**, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci USA* 2020; **117**: 9490-9496 [PMID: 32253318 DOI: 10.1073/pnas.2004168117]

8 **Chen X**, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, Men D, Huang Q, Liu Y, Yang B, Ding J, Li F. Detectable Serum Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load (RNAemia) Is Closely Correlated With Drastically Elevated Interleukin 6 Level in Critically Ill Patients With Coronavirus Disease 2019. *Clin Infect Dis* 2020; **71**: 1937-1942 [PMID: 32301997 DOI: 10.1093/cid/ciaa449]

9 **Pan Y**, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. *Lancet Infect Dis* 2020; **20**: 411-412 [PMID: 32105638 DOI: 10.1016/S1473-3099(20)30113-4]

10 **Cao B**, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* 2020; **382**: 1787-1799 [PMID: 32187464 DOI: 10.1056/NEJMoa2001282]

11 **Wang Y**, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; **395**: 1569-1578 [PMID: 32423584 DOI: 10.1016/S0140-6736(20)31022-9]

12 **Zou L**, Ruan F, Huang M, Liang L, Huang H, Hong Z, Yu J, Kang M, Song Y, Xia J, Guo Q, Song T, He J, Yen HL, Peiris M, Wu J. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020; **382**: 1177-1179 [PMID: 32074444 DOI: 10.1056/NEJMc2001737]

13 **Wang Y**, Zhang L, Sang L, Ye F, Ruan S, Zhong B, Song T, Alshukairi AN, Chen R, Zhang Z, Gan M, Zhu A, Huang Y, Luo L, Mok CKP, Al Gethamy MM, Tan H, Li Z, Huang X, Li F, Sun J, Zhang Y, Wen L, Li Y, Chen Z, Zhuang Z, Zhuo J, Chen C, Kuang L, Wang J, Lv H, Jiang Y, Li M, Lin Y, Deng Y, Tang L, Liang J, Huang J, Perlman S, Zhong N, Zhao J, Malik Peiris JS. Kinetics of viral load and antibody response in relation to COVID-19 severity. *J Clin Invest* 2020; **130**: 5235-5244 [PMID: 32634129 DOI: 10.1172/JCI138759]

14 **Wölfel R**, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, Niemeyer D, Jones TC, Vollmar P, Rothe C, Hoelscher M, Bleicker T, Brünink S, Schneider J, Ehmann R, Zwirglmaier K, Drosten C, Wendtner C. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020; **581**: 465-469 [PMID: 32235945 DOI: 10.1038/s41586-020-2196-x]

15 **Zheng S**, Fan J, Yu F, Feng B, Lou B, Zou Q, Xie G, Lin S, Wang R, Yang X, Chen W, Wang Q, Zhang D, Liu Y, Gong R, Ma Z, Lu S, Xiao Y, Gu Y, Zhang J, Yao H, Xu K, Lu X, Wei G, Zhou J, Fang Q, Cai H, Qiu Y, Sheng J, Chen Y, Liang T. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ* 2020; **369**: m1443 [PMID: 32317267 DOI: 10.1136/bmj.m1443]

16 **Baggio S**, L'Huillier AG, Yerly S, Bellon M, Wagner N, Rohr M, Huttner A, Blanchard-Rohner G, Loevy N, Kaiser L, Jacquerioz F, Eckerle I. SARS-CoV-2 viral load in the upper respiratory tract of children and adults with early acute COVID-19. *Clin Infect Dis* 2020; epub ahead of print [PMID: 32761228 DOI: 10.1093/cid/ciaa1157]

17 **Shi F**, Wu T, Zhu X, Ge Y, Zeng X, Chi Y, Du X, Zhu L, Zhu F, Zhu B, Cui L, Wu B. Association of viral load with serum biomakers among COVID-19 cases. *Virology* 2020; **546**: 122-126 [PMID: 32452410 DOI: 10.1016/j.virol.2020.04.011]

18 **Clementi N**, Ferrarese R, Tonelli M, Amato V, Racca S, Locatelli M, Lippi G, Silvestri G, Clementi M, Mancini N. Lower nasopharyngeal viral load during the latest phase of COVID-19 pandemic in a Northern Italy University Hospital. *Clin Chem Lab Med* 2020; **58**: 1573-1577 [PMID: 32598306 DOI: 10.1515/cclm-2020-0815]

19 **Kwon JS**, Kim JY, Kim MC, Park SY, Kim BN, Bae S, Cha HH, Jung J, Kim MJ, Lee MJ, Choi SH, Chung JW, Shin EC, Kim SH. Factors of Severity in Patients with COVID-19: Cytokine/Chemokine Concentrations, Viral Load, and Antibody Responses. *Am J Trop Med Hyg* 2020; **103**: 2412-2418

[PMID: 33124544 DOI: 10.4269/ajtmh.20-1110]
20 **Yu X**, Sun S, Shi Y, Wang H, Zhao R, Sheng J. SARS-CoV-2 viral load in sputum correlates with risk of COVID-19 progression. *Crit Care* 2020; **24**: 170 [PMID: 32326952 DOI: 10.1186/s13054-020-02893-8]
21 **Liu R**, Yi S, Zhang J, Lv Z, Zhu C, Zhang Y. Viral Load Dynamics in Sputum and Nasopharyngeal Swab in Patients with COVID-19. *J Dent Res* 2020; **99**: 1239-1244 [PMID: 32744907 DOI: 10.1177/0022034520946251]
22 **Zhou R**, Li F, Chen F, Liu H, Zheng J, Lei C, Wu X. Viral dynamics in asymptomatic patients with COVID-19. *Int J Infect Dis* 2020; **96**: 288-290 [PMID: 32437933 DOI: 10.1016/j.ijid.2020.05.030]
23 **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020; **159**: 81-95 [PMID: 32251668 DOI: 10.1053/j.gastro.2020.03.065]
24 **Azzi L**, Carcano G, Gianfagna F, Grossi P, Gasperina DD, Genoni A, Fasano M, Sessa F, Tettamanti L, Carinci F, Maurino V, Rossi A, Tagliabue A, Baj A. Saliva is a reliable tool to detect SARS-CoV-2. *J Infect* 2020; **81**: e45-e50 [PMID: 32298676 DOI: 10.1016/j.jinf.2020.04.005]
25 **Chen C**, Gao G, Xu Y, Pu L, Wang Q, Wang L, Wang W, Song Y, Chen M, Yu F, Yang S, Tang Y, Zhao L, Wang H, Wang Y, Zeng H, Zhang F. SARS-CoV-2-Positive Sputum and Feces After Conversion of Pharyngeal Samples in Patients With COVID-19. *Ann Intern Med* 2020; **172**: 832-834 [PMID: 32227141 DOI: 10.7326/M20-0991]
26 **Huang Y**, Chen S, Yang Z, Guan W, Liu D, Lin Z, Zhang Y, Xu Z, Liu X, Li Y. SARS-CoV-2 Viral Load in Clinical Samples from Critically Ill Patients. *Am J Respir Crit Care Med* 2020; **201**: 1435-1438 [PMID: 32293905 DOI: 10.1164/rccm.202003-0572LE]
27 **Pujadas E**, Chaudhry F, McBride R, Richter F, Zhao S, Wajnberg A, Nadkarni G, Glicksberg BS, Houldsworth J, Cordon-Cardo C. SARS-CoV-2 viral load predicts COVID-19 mortality. *Lancet Respir Med* 2020; **8**: e70 [PMID: 32771081 DOI: 10.1016/S2213-2600(20)30354-4]
28 **Arons MM**, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, Taylor J, Spicer K, Bardossy AC, Oakley LP, Tanwar S, Dyal JW, Harney J, Chisty Z, Bell JM, Methner M, Paul P, Carlson CM, McLaughlin HP, Thornburg N, Tong S, Tamin A, Tao Y, Uehara A, Harcourt J, Clark S, Brostrom-Smith C, Page LC, Kay M, Lewis J, Montgomery P, Stone ND, Clark TA, Honein MA, Duchin JS, Jernigan JA; Public Health–Seattle and King County and CDC COVID-19 Investigation Team. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. *N Engl J Med* 2020; **382**: 2081-2090 [PMID: 32329971 DOI: 10.1056/NEJMoa2008457]
29 **Huang JT**, Ran RX, Lv ZH, Feng LN, Ran CY, Tong YQ, Li D, Su HW, Zhu CL, Qiu SL, Yang J, Xiao MY, Liu MJ, Yang YT, Liu SM, Li Y. Chronological Changes of Viral Shedding in Adult Inpatients With COVID-19 in Wuhan, China. *Clin Infect Dis* 2020; **71**: 2158-2166 [PMID: 32445580 DOI: 10.1093/cid/ciaa631]
30 **Magleby R**, Westblade LF, Trzebucki A, Simon MS, Rajan M, Park J, Goyal P, Safford MM, Satlin MJ. Impact of SARS-CoV-2 Viral Load on Risk of Intubation and Mortality Among Hospitalized Patients with Coronavirus Disease 2019. *Clin Infect Dis* 2020 [PMID: 32603425 DOI: 10.1093/cid/ciaa851]
31 **Park SK**, Lee CW, Park DI, Woo HY, Cheong HS, Shin HC, Ahn K, Kwon MJ, Joo EJ. Detection of SARS-CoV-2 in Fecal Samples From Patients With Asymptomatic and Mild COVID-19 in Korea. *Clin Gastroenterol Hepatol* 2020; epub ahead of print [PMID: 32534042 DOI: 10.1016/j.cgh.2020.06.005]
32 **Yu F**, Yan L, Wang N, Yang S, Wang L, Tang Y, Gao G, Wang S, Ma C, Xie R, Wang F, Tan C, Zhu L, Guo Y, Zhang F. Quantitative Detection and Viral Load Analysis of SARS-CoV-2 in Infected Patients. *Clin Infect Dis* 2020; **71**: 793-798 [PMID: 32221523 DOI: 10.1093/cid/ciaa345]
33 **Blot M**, Jacquier M, Manoha C, Piroth L, Charles PE; Pneumochondrie study group. Alveolar SARS-CoV-2 Viral Load Is Tightly Correlated With Severity in COVID-19 ARDS. *Clin Infect Dis* 2021; **72**: e446-e447 [PMID: 32770223 DOI: 10.1093/cid/ciaa1172]
34 **Kim SE**, Jeong HS, Yu Y, Shin SU, Kim S, Oh TH, Kim UJ, Kang SJ, Jang HC, Jung SI, Park KH. Viral kinetics of SARS-CoV-2 in asymptomatic carriers and presymptomatic patients. *Int J Infect Dis* 2020; **95**: 441-443 [PMID: 32376309 DOI: 10.1016/j.ijid.2020.04.083]
35 **Argyropoulos KV**, Serrano A, Hu J, Black M, Feng X, Shen G, Call M, Kim MJ, Lytle A, Belovarac B, Vougiouklakis T, Lin LH, Moran U, Heguy A, Troxel A, Snuderl M, Osman I, Cotzia P, Jour G. Association of Initial Viral Load in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Patients with Outcome and Symptoms. *Am J Pathol* 2020; **190**: 1881-1887 [PMID: 32628931 DOI: 10.1016/j.ajpath.2020.07.001]
36 **Xu D**, Zhou F, Sun W, Chen L, Lan L, Li H, Xiao F, Li Y, Kolachalama VB, Wang X, Xu H. Relationship Between serum SARS-CoV-2 nucleic acid(RNAemia) and Organ Damage in COVID-19 Patients: A Cohort Study. *Clin Infect Dis* 2020; epub ahead of print [PMID: 32720678 DOI: 10.1093/cid/ciaa1085]
37 **Veyer D**, Kernéis S, Poulet G, Wack M, Robillard N, Taly V, L'Honneur AS, Rozenberg F, Laurent-Puig P, Bélec L, Hadjadj J, Terrier B, Péré H. Highly sensitive quantification of plasma SARS-CoV-2 RNA shelds light on its potential clinical value. *Clin Infect Dis* 2020; epub ahead of print [PMID: 32803231 DOI: 10.1093/cid/ciaa1196]
38 **Lin W**, Xie Z, Li Y, Li L, Wen C, Cao Y, Chen X, Ou X, Hu F, Li F, Tang X, Cai W. Association

between detectable SARS-COV-2 RNA in anal swabs and disease severity in patients with coronavirus disease 2019. *J Med Virol* 2021; **93**: 794-802 [PMID: 32672840 DOI: 10.1002/jmv.26307]

39 **Wang Y**, Liao B, Guo Y, Li F, Lei C, Zhang F, Cai W, Hong W, Zeng Y, Qiu S, Wang J, Li Y, Deng X, Li J, Xiao G, Guo F, Lai X, Liang Z, Wen X, Li P, Jiao Q, Xiang F, Wang Y, Ma C, Xie Z, Lin W, Wu Y, Tang X, Li L, Guan Y. Clinical Characteristics of Patients Infected With the Novel 2019 Coronavirus (SARS-Cov-2) in Guangzhou, China. *Open Forum Infect Dis* 2020; **7**: ofaa187 [PMID: 32577426 DOI: 10.1093/ofid/ofaa187]

40 **Kimball A**, Hatfield KM, Arons M, James A, Taylor J, Spicer K, Bardossy AC, Oakley LP, Tanwar S, Chisty Z, Bell JM, Methner M, Harney J, Jacobs JR, Carlson CM, McLaughlin HP, Stone N, Clark S, Brostrom-Smith C, Page LC, Kay M, Lewis J, Russell D, Hiatt B, Gant J, Duchin JS, Clark TA, Honein MA, Reddy SC, Jernigan JA; Public Health – Seattle & King County; CDC COVID-19 Investigation Team. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 377-381 [PMID: 32240128 DOI: 10.15585/mmwr.mm6913e1]

41 **Schwierzeck V**, König JC, Kühn J, Mellmann A, Correa-Martínez CL, Omran H, Konrad M, Kaiser T, Kampmeier S. First Reported Nosocomial Outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 in a Pediatric Dialysis Unit. *Clin Infect Dis* 2021; **72**: 265-270 [PMID: 33501962 DOI: 10.1093/cid/ciaa491]

42 **Xia XY**, Wu J, Liu HL, Xia H, Jia B, Huang WX. Epidemiological and initial clinical characteristics of patients with family aggregation of COVID-19. *J Clin Virol* 2020; **127**: 104360 [PMID: 32305025 DOI: 10.1016/j.jcv.2020.104360]

43 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

44 **Hagman K**, Hedenstierna M, Gille-Johnson P, Hammas B, Grabbe M, Dillner J, Ursing J. SARS-CoV-2 RNA in serum as predictor of severe outcome in COVID-19: a retrospective cohort study. *Clin Infect Dis* 2020 [PMID: 32856036 DOI: 10.1093/cid/ciaa1285]

45 **Prebensen C**, Myhre PL, Jonassen C, Rangberg A, Blomfeldt A, Svensson M, Omland T, Berdal JE. SARS-CoV-2 RNA in plasma is associated with ICU admission and mortality in patients hospitalized with COVID-19. *Clin Infect Dis* 2020 [PMID: 32888003 DOI: 10.1093/cid/ciaa1338]

46 **Hasanoglu I**, Korukluoglu G, Asilturk D, Cosgun Y, Kalem AK, Altas AB, Kayaaslan B, Eser F, Kuzucu EA, Guner R. Higher viral loads in asymptomatic COVID-19 patients might be the invisible part of the iceberg. *Infection* 2021; **49**: 117-126 [PMID: 33231841 DOI: 10.1007/s15010-020-01548-8]

47 **Kawasuji H**, Takegoshi Y, Kaneda M, Ueno A, Miyajima Y, Kawago K, Fukui Y, Yoshida Y, Kimura M, Yamada H, Sakamaki I, Tani H, Morinaga Y, Yamamoto Y. Transmissibility of COVID-19 depends on the viral load around onset in adult and symptomatic patients. *PLoS One* 2020; **15**: e0243597 [PMID: 33296437 DOI: 10.1371/journal.pone.0243597]

48 **Bermejo-Martin JF**, González-Rivera M, Almansa R, Micheloud D, Tedim AP, Domínguez-Gil M, Resino S, Martín-Fernández M, Ryan Murua P, Pérez-García F, Tamayo L, Lopez-Izquierdo R, Bustamante E, Aldecoa C, Gómez JM, Rico-Feijoo J, Orduña A, Méndez R, Fernández Natal I, Megías G, González-Estecha M, Carriedo D, Doncel C, Jorge N, Ortega A, de la Fuente A, Del Campo F, Fernández-Ratero JA, Trapiello W, González-Jiménez P, Ruiz G, Kelvin AA, Ostadgavahi AT, Oneizat R, Ruiz LM, Miguéns I, Gargallo E, Muñoz I, Pelegrin S, Martín S, García Olivares P, Cedeño JA, Ruiz Albi T, Puertas C, Berezo JÁ, Renedo G, Herrán R, Bustamante-Munguira J, Enríquez P, Cicuendez R, Blanco J, Abadia J, Gómez Barquero J, Mamolar N, Blanca-López N, Valdivia LJ, Fernández Caso B, Mantecón MÁ, Motos A, Fernandez-Barat L, Ferrer R, Barbé F, Torres A, Menéndez R, Eiros JM, Kelvin DJ. Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19. *Crit Care* 2020; **24**: 691 [PMID: 33317616 DOI: 10.1186/s13054-020-03398-0]

49 **Shlomai A**, Ben-Zvi H, Glusman Bendersky A, Shafran N, Goldberg E, Sklan EH. Nasopharyngeal viral load predicts hypoxemia and disease outcome in admitted COVID-19 patients. *Crit Care* 2020; **24**: 539 [PMID: 32873316 DOI: 10.1186/s13054-020-03244-3]

50 **Ra SH**, Lim JS, Kim GU, Kim MJ, Jung J, Kim SH. Upper respiratory viral load in asymptomatic individuals and mildly symptomatic patients with SARS-CoV-2 infection. *Thorax* 2021; **76**: 61-63 [PMID: 32963115 DOI: 10.1136/thoraxjnl-2020-215042]

51 **Faíco-Filho KS**, Passarelli VC, Bellei N. Is Higher Viral Load in SARS-CoV-2 Associated with Death? *Am J Trop Med Hyg* 2020; **103**: 2019-2021 [PMID: 32996443 DOI: 10.4269/ajtmh.20-0954]

52 **Chen L**, Wang G, Long X, Hou H, Wei J, Cao Y, Tan J, Liu W, Huang L, Meng F, Wang N, Zhao J, Huang G, Sun Z, Wang W, Zhou J. Dynamics of Blood Viral Load Is Strongly Associated with Clinical Outcomes in Coronavirus Disease 2019 (COVID-19) Patients: A Prospective Cohort Study. *J Mol Diagn* 2021; **23**: 10-18 [PMID: 33122141 DOI: 10.1016/j.jmoldx.2020.10.007]

53 **Fajnzylber J**, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, Worrall D, Giguel F, Piechocka-Trocha A, Atyeo C, Fischinger S, Chan A, Flaherty KT, Hall K, Dougan M, Ryan ET, Gillespie E, Chishti R, Li Y, Jilg N, Hanidziar D, Baron RM, Baden L, Tsibris AM, Armstrong KA, Kuritzkes DR, Alter G, Walker BD, Yu X, Li JZ; Massachusetts Consortium for Pathogen Readiness. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nat Commun* 2020; **11**:

5493 [PMID: 33127906 DOI: 10.1038/s41467-020-19057-5]
54 **Zhou S**, Yang Y, Zhang X, Li Z, Liu X, Hu C, Chen C, Wang D, Peng Z. Clinical Course of 195 Critically Ill COVID-19 Patients: A Retrospective Multicenter Study. *Shock* 2020; **54**: 644-651 [PMID: 32826818 DOI: 10.1097/SHK.0000000000001629]
55 **Maltezou HC**, Raftopoulos V, Vorou R, Papadima K, Mellou K, Spanakis N, Kossyvakis A, Gioula G, Exindari M, Froukala E, Martinez-Gonzalez B, Panayiotakopoulos G, Papa A, Mentis A, Tsakris A. Association Between Upper Respiratory Tract Viral Load, Comorbidities, Disease Severity, and Outcome of Patients With SARS-CoV-2 Infection. *J Infect Dis* 2021; **223**: 1132-1138 [PMID: 33388780 DOI: 10.1093/infdis/jiaa804]
56 **Bitker L**, Dhelft F, Chauvelot L, Frobert E, Folliet L, Mezidi M, Trouillet-Assant S, Belot A, Lina B, Wallet F, Richard JC. Protracted viral shedding and viral load are associated with ICU mortality in Covid-19 patients with acute respiratory failure. *Ann Intensive Care* 2020; **10**: 167 [PMID: 33301059 DOI: 10.1186/s13613-020-00783-4]
57 **Carrasquer A**, Peiró ÓM, Sanchez-Gimenez R, Lal-Trehan N, Del-Moral-Ronda V, Bonet G, Gutierrez C, Fort-Gallifa I, Martin-Grau C, Benavent C, Vidal F, Bardají A. Lack of Association of Initial Viral Load in SARS-CoV-2 Patients with In-Hospital Mortality. *Am J Trop Med Hyg* 2020; **104**: 540-545 [PMID: 33357280 DOI: 10.4269/ajtmh.20-1427]
58 **de la Calle C**, Lalueza A, Mancheño-Losa M, Maestro-de la Calle G, Lora-Tamayo J, Arrieta E, García-Reyne A, Losada I, de Miguel B, Díaz-Simón R, López-Medrano F, Fernández-Ruiz M, Carretero O, San Juan R, Aguado JM, Lumbreras C. Impact of viral load at admission on the development of respiratory failure in hospitalized patients with SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis* 2021; **40**: 1209-1216 [PMID: 33409832 DOI: 10.1007/s10096-020-04150-w]
59 **Bryan A**, Fink SL, Gattuso MA, Pepper G, Chaudhary A, Wener MH, Morishima C, Jerome KR, Mathias PC, Greninger AL. SARS-CoV-2 Viral Load on Admission Is Associated With 30-Day Mortality. *Open Forum Infect Dis* 2020; **7**: ofaa535 [PMID: 33349793 DOI: 10.1093/ofid/ofaa535]
60 **Choudhuri J**, Carter J, Nelson R, Skalina K, Osterbur-Badhey M, Johnston A, Goldstein D, Paroder M, Szymanski J. SARS-CoV-2 PCR cycle threshold at hospital admission associated with patient mortality. *PLoS One* 2020; **15**: e0244777 [PMID: 33382805 DOI: 10.1371/journal.pone.0244777]
61 **Shenoy S**. Coronavirus (Covid-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality. *Inflamm Res* 2020; **69**: 1077-1085 [PMID: 32767095 DOI: 10.1007/s00011-020-01389-z]
62 **Chu CM**, Poon LL, Cheng VC, Chan KS, Hung IF, Wong MM, Chan KH, Leung WS, Tang BS, Chan VL, Ng WL, Sim TC, Ng PW, Law KI, Tse DM, Peiris JS, Yuen KY. Initial viral load and the outcomes of SARS. *CMAJ* 2004; **171**: 1349-1352 [PMID: 15557587 DOI: 10.1503/cmaj.1040398]
63 **Peiris JS**, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS, Chan KH, Ng JS, Zheng BJ, Ng WL, Lai RW, Guan Y, Yuen KY; HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; **361**: 1767-1772 [PMID: 12781535 DOI: 10.1016/s0140-6736(03)13412-5]
64 **Oh MD**, Park WB, Choe PG, Choi SJ, Kim JI, Chae J, Park SS, Kim EC, Oh HS, Kim EJ, Nam EY, Na SH, Kim DK, Lee SM, Song KH, Bang JH, Kim ES, Kim HB, Park SW, Kim NJ. Viral Load Kinetics of MERS Coronavirus Infection. *N Engl J Med* 2016; **375**: 1303-1305 [PMID: 27682053 DOI: 10.1056/NEJMc1511695]
65 **Liu Y**, Liao W, Wan L, Xiang T, Zhang W. Correlation Between Relative Nasopharyngeal Virus RNA Load and Lymphocyte Count Disease Severity in Patients with COVID-19. *Viral Immunol* 2020; epub ahead of print [PMID: 32297828 DOI: 10.1089/vim.2020.0062]
66 **Lucas C**, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, Ellingson MK, Mao T, Oh JE, Israelow B, Takahashi T, Tokuyama M, Lu P, Venkataraman A, Park A, Mohanty S, Wang H, Wyllie AL, Vogels CBF, Earnest R, Lapidus S, Ott IM, Moore AJ, Muenker MC, Fournier JB, Campbell M, Odio CD, Casanovas-Massana A; Yale IMPACT Team, Herbst R, Shaw AC, Medzhitov R, Schulz WL, Grubaugh ND, Dela Cruz C, Farhadian S, Ko AI, Omer SB, Iwasaki A. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020; **584**: 463-469 [PMID: 32717743 DOI: 10.1038/s41586-020-2588-y]
67 **Han H**, Ma Q, Li C, Liu R, Zhao L, Wang W, Zhang P, Liu X, Gao G, Liu F, Jiang Y, Cheng X, Zhu C, Xia Y. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg Microbes Infect* 2020; **9**: 1123-1130 [PMID: 32475230 DOI: 10.1080/22221751.2020.1770129]
68 **Li L**, Liang Y, Hu F, Yan H, Li Y, Xie Z, Huang L, Zhao J, Wan Z, Wang H, Shui J, Cai W, Tang S. Molecular and serological characterization of SARS-CoV-2 infection among COVID-19 patients. *Virology* 2020; **551**: 26-35 [PMID: 33011520 DOI: 10.1016/j.virol.2020.09.008]
69 **Fourati S**, Hue S, Pawlotsky JM, Mekontso-Dessap A, de Prost N. SARS-CoV-2 viral loads and serum IgA/IgG immune responses in critically ill COVID-19 patients. *Intensive Care Med* 2020; **46**: 1781-1783 [PMID: 32572527 DOI: 10.1007/s00134-020-06157-5]
70 **Widders A**, Broom A, Broom J. SARS-CoV-2: The viral shedding vs infectivity dilemma. *Infect Dis Health* 2020; **25**: 210-215 [PMID: 32473952 DOI: 10.1016/j.idh.2020.05.002]
71 **Weissleder R**, Lee H, Ko J, Pittet MJ. COVID-19 diagnostics in context. *Sci Transl Med* 2020; **12**: eabc1931 [PMID: 32493791 DOI: 10.1126/scitranslmed.abc1931]
72 **Loeffelholz MJ**, Tang YW. Laboratory diagnosis of emerging human coronavirus infections - the state of the art. *Emerg Microbes Infect* 2020; **9**: 747-756 [PMID: 32196430 DOI:

10.1080/22221751.2020.1745095]
73 **Bisoffi Z**, Pomari E, Deiana M, Piubelli C, Ronzoni N, Beltrame A, Bertoli G, Riccardi N, Perandin F, Formenti F, Gobbi F, Buonfrate D, Silva R. Sensitivity, Specificity and Predictive Values of Molecular and Serological Tests for COVID-19: A Longitudinal Study in Emergency Room. *Diagnostics (Basel)* 2020; **10**: 669 [PMID: 32899333 DOI: 10.3390/diagnostics10090669]
74 **Fung B**, Gopez A, Servellita V, Arevalo S, Ho C, Deucher A, Thornborrow E, Chiu C, Miller S. Direct Comparison of SARS-CoV-2 Analytical Limits of Detection across Seven Molecular Assays. *J Clin Microbiol* 2020; **58**: e01535-20 [PMID: 32651238 DOI: 10.1128/JCM.01535-20]
75 **Suo T**, Liu X, Feng J, Guo M, Hu W, Guo D, Ullah H, Yang Y, Zhang Q, Wang X, Sajid M, Huang Z, Deng L, Chen T, Liu F, Xu K, Liu Y, Xiong Y, Chen G, Lan K, Chen Y. ddPCR: a more accurate tool for SARS-CoV-2 detection in low viral load specimens. *Emerg Microbes Infect* 2020; **9**: 1259-1268 [PMID: 32438868 DOI: 10.1080/22221751.2020.1772678]
76 **Cao Y**, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G, Wang W. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov* 2020; **6**: 11 [PMID: 32133153 DOI: 10.1038/s41421-020-0147-1]
77 **Gupta A**, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**: 1017-1032 [PMID: 32651579 DOI: 10.1038/s41591-020-0968-3]
78 **Kleiboeker S**, Cowden S, Grantham J, Nutt J, Tyler A, Berg A, Altrich M. SARS-CoV-2 viral load assessment in respiratory samples. *J Clin Virol* 2020; **129**: 104439 [PMID: 32674034 DOI: 10.1016/j.jcv.2020.104439]

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META-ANALYSIS

COVID-19 and resuscitation: La tournée of traditional Chinese medicine?

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Abstract

BACKGROUND

As it has been established in previous publications of the author, the current extra-hospital statistics referring to cardiopulmonary resuscitation (CPR) are far from being minimally satisfactory (14%-17% success). Since the appearance of acquired immune deficiency syndrome, its application has been increasingly undermined as other subsequent pandemics (H1N1, Ebola, coronavirus disease 2019) seriously infringing lay rescuers intervention during classical CPR steps (mouth-to-mouth ventilation), forcing to modify vital support protocols. Both KI-1 Yong quan and PC-9 Zhong chong alternative rescue maneuvers could come to aid those victims of impending death situation due to both cardiac arrest or stroke, upgrading current survival rates of said unfortunate patients.

AIM

To validate a complementary resuscitation maneuver originated in Chinese Medicine knowledge, carefully integrated into international CPR protocols [*World Journal of Critical Care Medicine* (*WJCCM*), August 2013].

METHODS

The model to verify its statistical validity of quoted research was the Retrospective Cohort Study, which redeems the "semiotic paradigm" that gave rise to medical semiotics. Its value strives in the differential detail if the deceased patients are considered the control group instead of the patients that may be deceased. Thus, combining the semiotic paradigm with the Retrospective Cohort Study allows us to manage the collateral potential lethal effects of the random process in cases of extreme emergencies.

RESULTS

The statistic results provided by the methodological analysis of this work were previously published in *WJCCM* August 2013, ISSN 2220-3141). In a total of 89 patients in which the Yong quan maneuver was tested, 75 survived and 14 died.

manuscript

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In order to compare this data with the percentages of survivors in the other maneuvers, we stipulate the assumption that if 89 patients are the 100% of the sample, how many patients would survive if the survival rate is 6.4% in CPR, 30% in defibrillation and 48% in CPR + defibrillation. By this way we obtained the approximate values of patients that would survive when applying these classical resuscitation maneuvers. Then we obtained the format of the tables to perform the exact Fisher test with the help of a statistical processor; the consequent result in a valuation of $P < 0.0001$ was considered "extremely statistically significant".

CONCLUSION

The author herein provides a methodological–statistical analysis of such contribution which does not imply any cost at all and could even help prevent the withdrawal of classical CPR practices.

Key Words: COVID-19; Cardiopulmonary resuscitation protocol; Contingency measures; KI-1 Yong quan resuscitation maneuver; Pandemic

Core Tip: Against current pandemic scenario, the author analyzes the possible difficulties that could occur on essential life support protocols as cardiopulmonary resuscitation (CPR). As happened with the previous H1N1 pandemic, from when it was decided to postpone the "kiss to life" (mouth ventilation) giving priority to the precordial massage, coronavirus disease 2019 global situation could drastically reduce survival rates due to CPR and life-support protocols. For this reason, the author insists on an additional complementary resuscitation maneuver from Traditional Chinese Medicine - already published by the *World Journal of Critical Care Medicine* in Beijing in August 2013, in order to improve the rescue success in sudden death and out-of-hospital cardiac arrest.

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INTRODUCTION

The cardiopulmonary resuscitation (CPR) maneuver can be considered to constitute the most important medical act that exists in universal medicine. Both in the East and in the West, its medical significance acquired such importance that even those who are not practicing physicians or involved otherwise in Medical or Health Sciences manage to be authorized once they have been instructed in the "chain of events" incorporated into the life support protocol sequences[1].

Following the American Heart Association, the CPR aims - understood as the reversal of clinical death - are to preserve life, restore health and limit disabilities, although such benefits can, in fact, only be achieved by a limited number of victims, whose dispositions and pathologies are more often than not totally unknown to the eventual rescuers, whose mission, in turn, is to save them from such a dire situation[2,3].

According to World Health Organization (WHO), more than 23% of all causes of death are due to cardiovascular factors. If to that percentage we add up that of cerebrovascular diseases, the total surpasses 30% of all existing causes of death. For this reason, by the end of 2020, beyond this gloomy pandemic crisis that affects us, the number of deaths due to cardiac arrest could reach a staggering 30000000 deaths per year[4]. Taking a current example, the results of the extrahospital rescues only reaches the meager figure of 6.5% with precordial massage and of 17%, when defibrillation is used. If the total death toll during World War II was estimated to be around 50,000,000 along the course of four years of devastation, it should not be difficult for us to consider that we are facing a true sanitary catastrophe[4,5].

MATERIALS AND METHODS

Materials

KI-1 Yong quan acupuncture point location: KI-1 Yong quan is located in the sole of each foot, in the place where it makes its plantar flexion. Dividing a line that runs all across the foot´s sole, the point is found at the junction between the anterior and the middle third of the plantar fascia level at its deepest position (see Figures 1 and 2)[1,4,5].

Physiological functions of KI-1 Yong quan point: According to chapter 5 of the *Ling Shu*, KI-1 Yong quan is considered the Tsing-well point of the kidney meridian and the "root" of the *Shao Yin* level (conformed by kidneys and heart). Said quotation explains by itself the remarkable influence of KI-1 Yong quan overall cardiac physiology[1,5]. It is the vortex where the Terrestrial Qi ascends into our bodies for nurture the *zhang*, mostly in that organs placed in the upper part of the torso that maintain the essential vital functions due to their continuous function (heart and lungs).

Moreover, KI-1 Yong quan is the main place for the ascending Yin Qi from the earth into our bodies. Therefore, this kind of energy will nurture the *zhang*, especially those organs placed at the highest (Yang) part of the torso, essential due to their vital function which cannot be interrupted: heart and lungs, providing them Yang Qi for a perfect biological equilibrium[1,4,5].

Topographic anatomy of PC-9 Zhong chong acupuncture point: Traditionally, this point is located at the tip of the middle finger, mostly to bleed it under emergency conditions. Rather curiously, that finger is also known in Spanish has "*cordial*" or "*heart finger*", showing a nominative association with its anatomic-functional value between it and the organ it protects[4].

Physiological Functions of PC-9 Zhong chong: PC-9 Zhong chong is the Tsing-well point of the "Heart Protector" or Pericardium meridian. As such, it is a Heart stimulating source that explains the therapeutic possibility of alleviating cardiovascular conditions. Its effect enables PC-9 to restore the cardiac pacemaker by direct stimulation over the sinoauricular node (vide infra Figure 3).

Scientific validation of PC-9 Zhong chong in bilateral double amputees as well as healthy volunteers has been successful for applying as supplementary resuscitation maneuver equivalent as the KI-1 Yong quan praxis[4].

Next, a formalized protocol project was submitted to *World Journal of Critical Care Medicine* in 2016 in order to integrate said acupunctural points into the CPR sequence.

Stages of the The International Liaison Committee on Resuscitation - CPR sequence ("chain")

See below Figure 4: (1) Prior to the application of chest massage: Assess the victim's state of consciousness and lung-heart failure; (2) Seek help (call 911), and/or apply KI-1 Yong quan/PC-9 Zhong chong in situations in which it is impossible to start the The International Liaison Committee on Resuscitation (ILCOR) protocol: If the victim is trapped in a car crash, an overturned car, a landslide, or there is a massive number of victims or a catastrophe; or Delayed CPR due to physical barriers to execute chest massage or exhausted rescuers due to catastrophic number of victims, *etc*[5]; (3) During chest compression: during the precordial massage, KI-1 Yong quan could be simultaneously stimulated by a third rescuer in the sole of the victim's foot[5]; (4) During defibrillator application: prior to the electric shock, activate KI-1 Yong quan through placing needles in both soles before defibrillation (or at PC-9 Zhong chong if the patient is a bilateral amputee)[1,5]; and (5) Unsuccessful basic and advanced CPR: KI-1 Yong quan and PC-9 Zhong chong stimulation become the "golden standard" for reverting legal clinical death[5].

In a very interesting paper, Bester and Kodish[6] address the issue in a crucial way providing a moral justification for CPR application. Undoubtedly, there should be no need to gauge the value of taking this decisive action during impending-life situations. The clinical version of Bester and Kodish[6] makes it clear that they abide by the moral imperative of rescue, except for very specific situations, called "Do Not Resuscitate" orders, in force in many countries, although there is no such provision in Argentina.

Methodological statistical approach – KI-1 Yong quan maneuver benefit

Randomness principle always request to minimize uncertainty[5,7].

In spite of what has been stated, comprehending that we might not eventually be able to solve every single question, we have given statistical priority to prove the following affirmation proposed between two hypotheses: Ho (null hypothesis): its

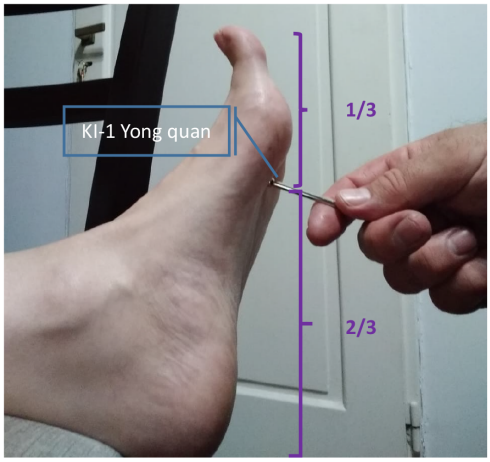

Figure 1 KI-1 Yong quan resuscitation maneuver: Side view.

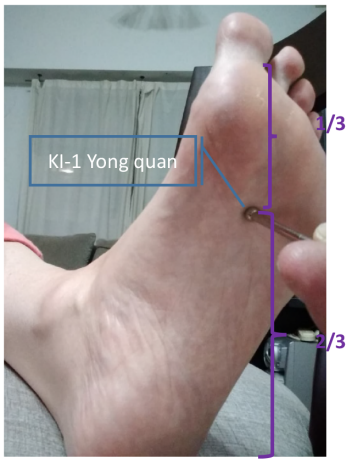

Figure 2 KI-1 Yong quan resuscitation maneuver: Front view.

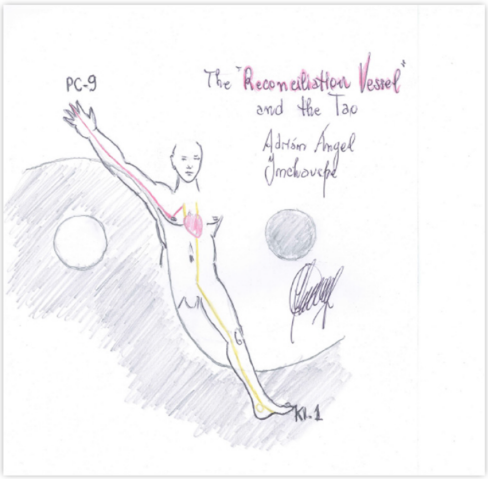

Figure 3 The reconciliation vessel and the Tao.

affirmation determines the lack of association between the variables under study; Ha (alternative hypothesis): its affirmation implies some degree of relationship between said variables[5,7].

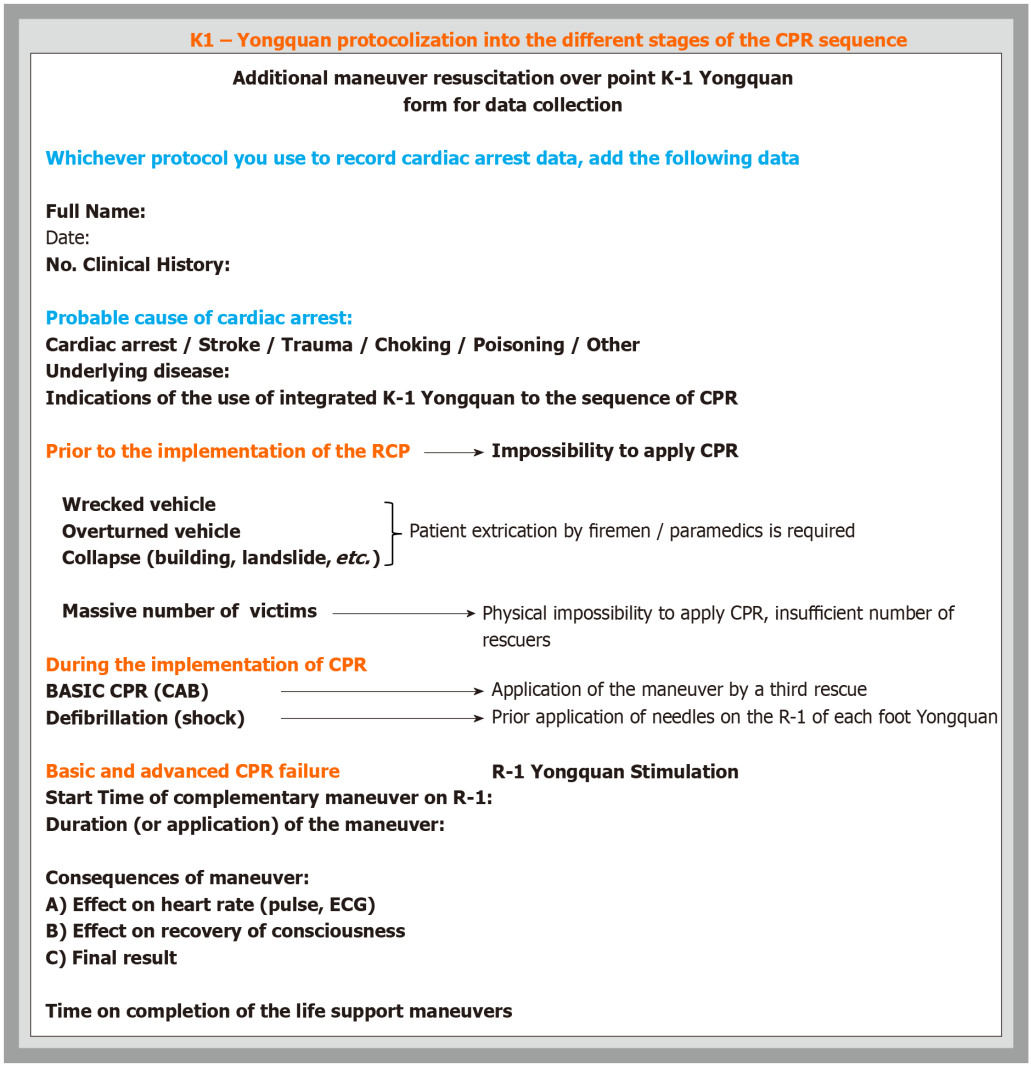

Figure 4 KI-1 Yong quan Protocol integrated to International Liaison Committee on Resuscitation: Cardiopulmonary resuscitation "Action chain". Citation: Inchauspe AA. Drawing the Yongquan protocol into the different stages of the cardiopulmonary resuscitation sequence. *World J Crit Care Med* 2013; 2: 17-20. Copyright © The Author(s) 2013. Published by Baishideng Publishing Group Inc[5].

We first compared the group assisted by CPR precordial massage (6.5% response) and those rescued by KI-1 Yong quan resuscitation maneuver (84.84% response):

$|PA - PB| = |0.064 - 0.85| = 0.786 < SE\ (0.05) \times 1.96 = 0.098$.

This fact theoretically proves that KI-1 Yong quan resuscitation method success does not depend on fate.

Afterwards, we compared the use of CPR defibrillation (48% response) against the KI-1 Yong quan resuscitation maneuver (84.84% response):

$|PA - PB| = |0.48 - 0.84| = 0.36 < SE\ (0.0076) \times 1.96 = 0.0148)$.

Thus, $[PA' - PB] = 0.36$.

Quoted analysis also proves to be statistically significant, favoring the KI-1 Yong quan resuscitation maneuver by means of this comparative analysis[5,7].

If we consider the control group conformed by the already deceased people instead of the patients that prospectively may be deceased, thus the Retrospective Cohort Study will safely solve this "*statistical issue*", allowing us to manage potential lethal effects, thus eliminating the fateful impairment found in random contingency, mostly in these cases under extreme emergency situation[5,7].

RESULTS

As to its statistical verification, several sequences of survival rates were presented, the first 7 of which were published in Health (2015), the 8th one in the *World Journal of Critical Care Medicine* (2016) and the 9th and last sampling, at the Health Care Summit

Congress in Dublin (June 2018) (see below Figure 5).

About the last ninth statistic, from a total of 89 patients in which KI-1 Yong quan maneuver was tested, 75 victims survived and 14 died. In order to compare this data with the percentages of survivors in the other rescue protocols, we assume that if 89 patients represent the 100% of the sample, how many patients would survive if the successful CPR rate would be 6.4% after chest massage (see Figure 6); 30% post-defibrillation (see Figure 7) or 48% that kept alive after CPR +defibrillation carried out jointly (see Figure 8).

So we then obtained the approximate values of victims that would survive when applying these resuscitation maneuvers in round figures in order to facilitate calculations. From the total of patients (89 cases), we subtracted the survivors to obtained the mortality rates[7].

The Graph Pad site showed a two-tailed *P* value, recommending us to analyze the sample with dichotomous variables so as to obtain more reliable deductions (for a more detailed mathematical explanation, please refer to "*Yongquan Maneuver´s Oddysey: Current Validation Of Its Significance Of P Through The Fisher's Exact Test For Dichotomous Variables*", published by Acta Scientific Paediatrics[7].

Thus we then obtained the format of the tables to perform the exact Fisher test, solved by a statistic mathematical processor; the results were located at the side of each table. As we can see, the Fisher exact test obtained a statistic valuation of $P < 0.0001$, considering quoted outcome as "extremely statistically significant"[7].

DISCUSSION

As was shown when stating Randomness in this problem - that means, under such extremely emergency situation - the control group would not only not benefit from a second chance of survival during imminent death, but also such therapeutic discrimination would also imply a fatal, collateral or unwanted results for the members of that group, doomed by this investigation model[4].

Regarding adding the complementary maneuver on KI-1 Yong quan / PC-9 Zhong chong into the classic CPR protocol, what has previously been stated contrasts with the essence of that principle. If data on fatal contingency is previously known in a study in which patients will be randomly discarded, such methodology will clearly impair them of the KI-1 maneuver benefit in case of basic and advanced CPR failure.

Random non-intervention practiced on such a group would inevitably lead to a most serious ethical problem as not providing adequate assistance to those patients who have been "sorted out".

As stated in Article 32 of *the Declaration of Helsinki VI on Ethical Human Rights* should not be forgotten when it states that "*In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, reestablishing health or alleviating suffering*"[8].

Although it is true that the article refers to informed consent, it is understood that these are not cases of extreme urgency, where the essential criterion of saving life acquires paramount significance.

Now let's ethically confront this right to life with the autonomy rights to which several Western countries refer, in order to evaluate priorities when determining the importance of individual opinion and its impact on rescue efforts at a global level.

The principle of patient autonomy

Patient autonomy is generally ethically respected. However, in Argentina in the case of CPR, the rescuer's criteria prevail, refusing to leave the victim without help. Said right requires a patient who can consent or refuse CPR, but without deterioration from depression, neuropsychiatric medication, or co-occurring illnesses. In any case, despite the fact that this right remains in force in many countries, a Research Ethics Committee must first assess the real possibility of restoring the patient's health[9].

Advance directives and living wills

Advance directive expresses a person's last wishes, or preferences regarding his or her end-of-life care; in many cases, questionably limiting the CPR rescue.

Quoted item is conformed by the directions from patients to physicians about the provision of medical care during a terminal illness course or when confronted with the impossibility to make proper decisions. It constitutes a clear evidence of the patient's

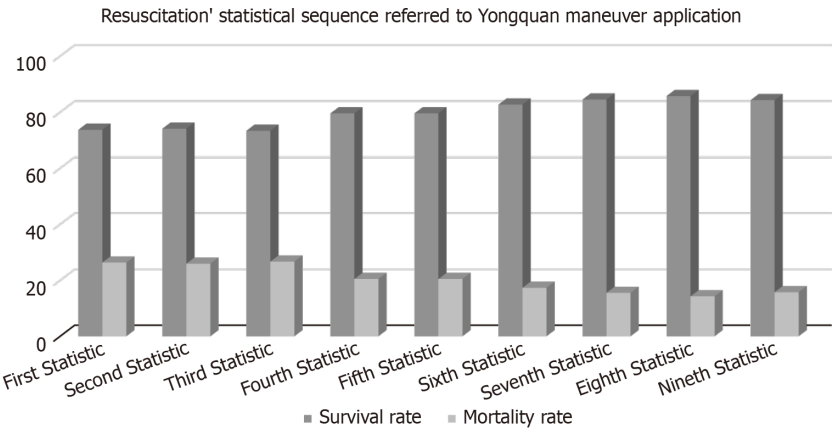

Figure 5 Statistical Sequence Referred to KI-1 Yong quan maneuver application (referred above). Citation: Inchauspe AA, Inchauspe M. "Yongquan Maneuver´s Odyssey: Current Validation of Its Significance of P Through the Fisher's Exact Test for Dichotomous Variables". *Acta Scientific Paediatrics* 2019; 2: 53-60. Copyright ©The Author(s) 2013. Published by Acta Scientific Paediatrics[7].

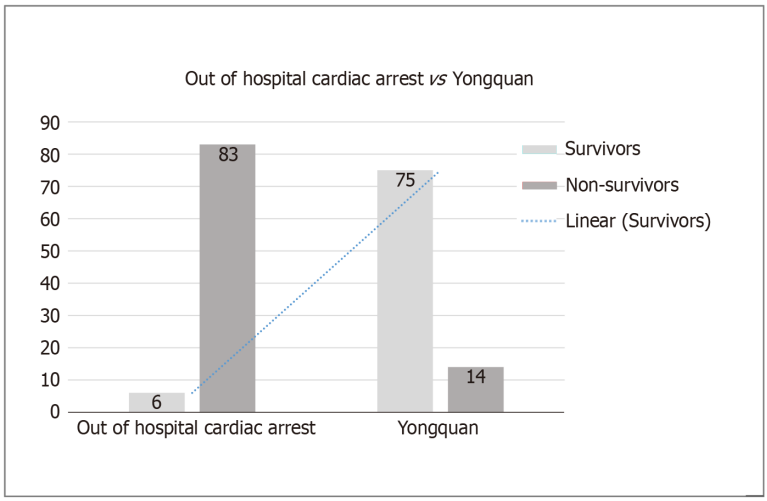

Figure 6 Out of Hospital Cardiac Arrest vs. Yong quan Survivors' tendency. Citation: Inchauspe AA, Inchauspe M. "Yongquan Maneuver´s Odyssey: Current Validation of Its Significance of P Through the Fisher's Exact Test for Dichotomous Variables". *Acta Scientific Paediatrics* 2019; 2: 53-60. Copyright ©The Author(s) 2013. Published by Acta Scientific Paediatrics[7].

wishes and can be legally enforced[9].

In Argentina, life is an immanent right that does not only depend exclusively on patients. Neither the victims nor rescuers can change the legal consensus of CPR protocols in an emergency state.

CPR suspension would only be considered in those terminal conditions determined in outdoors trauma triage score (slaughter, traumatic hemicorporectomy, massive loss of brain mass)[10] or indoors hospitals, so a Bioethical Committee can carefully study each particular case in order to suggest vital support suspension due to irreversible suffering conditions.

Despite the above-mentioned "*non-resuscitation orders*" based on the law in force of each country, the KI-1 Yong quan resuscitation maneuver would be useful as long as it is promptly applied, with the following considerations: (1) Currently, according to WHO, 23% of overall causes death result by cardiovascular origin[11]; (2) If we sum up the 7.6% of cerebrovascular casualties, we reach an average of 30% of overall causes of death[5,7]; (3) PC-9 Zhong Chong's proposal on the protocol involving Chinese acupuncture points has a dual purpose: The first and most important is the inclusion of those individuals who suffered bilateral amputation, which in this way could benefit greatly from the stimulation of this alternative point before the failure of the basic and/or advanced CPR; and The second is to have another stimulation alternative that provides an additional opportunity to rescue patients in a situation of imminent death due to sudden death or cardiac arrest[4,5,7].

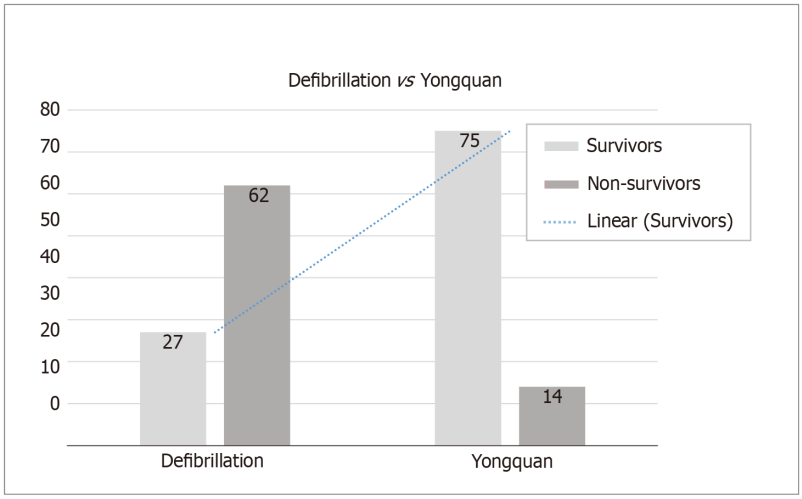

Figure 7 Defibrillation *vs* Yong quan Survivors' tendency. Citation: Inchauspe AA, Inchauspe M. "Yongquan Maneuver´s Odyssey: Current Validation of Its Significance of P Through the Fisher's Exact Test for Dichotomous Variables". *Acta Scientific Paediatrics* 2019; 2: 53-60. Copyright ©The Author(s) 2013. Published by Acta Scientific Paediatrics[7].

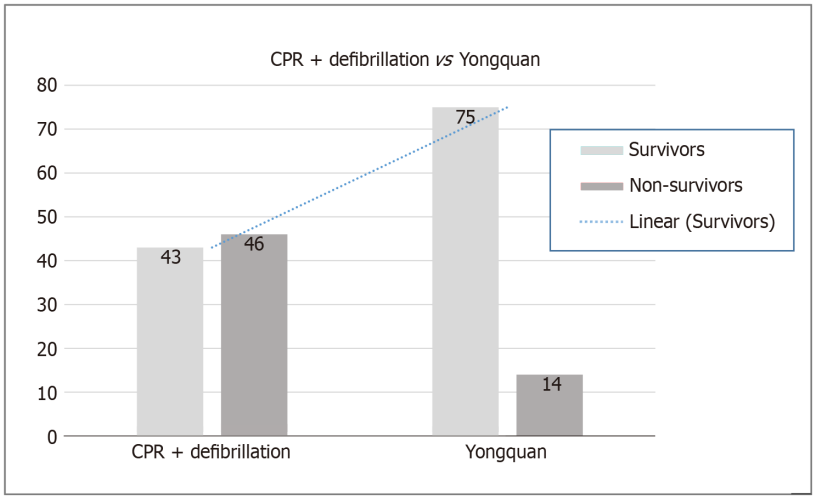

Figure 8 Cardiopulmonary resuscitation + defibrillation *vs* Yong quan Survivors' tendency. CPR: cardiopulmonary resuscitation. Citation: Inchauspe AA, Inchauspe M. "Yongquan Maneuver´s Odyssey: Current Validation of Its Significance of P Through the Fisher's Exact Test for Dichotomous Variables". *Acta Scientific Paediatrics* 2019; 2: 53-60. Copyright ©The Author(s) 2013. Published by Acta Scientific Paediatrics[7].

We must remember that diabetes affects almost 10% of the world's population, increasing the risk of cardiovascular and cerebrovascular diseases from 50% to 80% in these patients[11]. Consequently, every three seconds, a diabetic foot is amputated in the world[5,7].

In Argentina, two people per hour (that is, 54 per day and more than 20000 per year) will experience sudden death; the global annual average attributed solely to sudden death ranges from 5 to 6 million victims[7].

In infants, the sudden death mortality is over 35.2 deaths per 100000 live births in 2018 (Figure 9). Again, these children lack true capacity to accept or reject any vital protocol to decide the life-saving benefit provided by the CPR protocol[12].

Plausible solution to the dilemma of applying the CPR protocol with or without prior informed consent:

We have analyzed this particular situation with the Research Ethics Committee of the Province of Buenos Aires, in order to settle the dilemma in face of the always surprising and unexpected appearance of a sudden death scenario.

Given that the patient under these conditions is clearly unable to decide the application of this universal protocol, a possible solution emerged upon scientific consensus once the life support protocol and its modifications had been accepted by

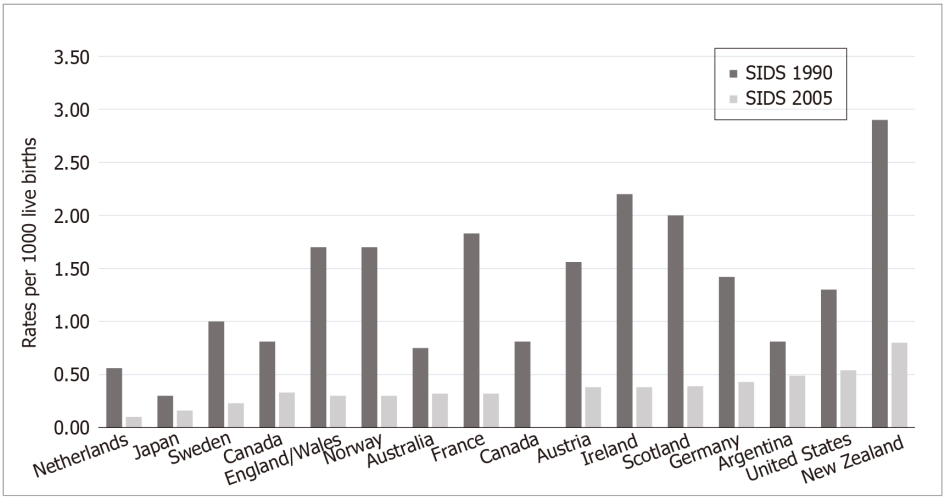

Figure 9 International sudden infant death syndrome rates, ordered from lowest to highest sudden infant death syndrome rates, National Center for Education in Maternal and Child Health – Georgetown University. SIDS: Sudden infant death syndrome.

the Committee of Scientific Research or Regional Bioethics One acceptable solution lies in spreading through local/regional mass media (also adding social networks) the future establishment of the protocol in question. The media diffusion of said novelty should be applied only for some hospitals in the area, leaving citizens with their free decision where to turn in case of extreme need. Likewise, it will be clarified that the health emergency services will also apply said life support scheme within their area of influence.

The information will remain valid for at least one week on the mass media networks. In this way, it is possible to comply with the objective of informing the population of the future intervention with the CPR modality agreed by the experts of the region.

Research committees must be very efficient while organizing educational programs and developing hospital guidelines. Again, ethical and moral dimensions of such decision should pay special attention not to transfer an even more serious offence to the rescue group: That of abandoning the patient[5,7,9,11].

CONCLUSION

In my country there exists so far no “Do Not Resuscitate” order; consequently, any evasion of the application of CPR in a condition of cardiac arrest shall be interpreted as “abandonment of the patient”; and the life support maintenance time – as long as it has arrived in time at the scene, maintaining suitable oxygen saturation – shall not be less than 45 minutes of rescue, before considering it failed.

The contribution of the complementary maneuver on the KI-1 Yong quan and /or PC-9 Zhong chong acupuncture points is neither intended to replace nor to interrupt the CPR international protocol, but to provide an alternative way of upgrading heart stoppage survival rates when the ILCOR-CPR protocol has failed.

Cotler[9] states very well that in his work “The” do not resuscitate "order; clinical and ethical rationale and implications” that the provision of CPR and do-not-resuscitate orders (DNRs) raises a current legal controversy regarding the need to obtain consented permission during a crucial moment to act efficiently during such a critical situation. Although patients' values or previous determinations are relevant, particularly those related to unwanted reasons to deny CPR rescuers decisions concerning CPR often must be made within seconds, most of the time without knowing patients´ directives[13].

On the other hand, those conditions that could presuppose the denial of the initiation of CPR (terminal illnesses, “therapeutic fierceness”, *etc.*) imply a deep knowledge of the philosophical controversy they pose, which may not necessarily be within the reach of most of the usual rescuers, be them firefighters or security personnel, professors or teachers, relatives, friends or unknown laypersons who learned life support protocols. Compliance under the spirit of a CPR protocol must not

carry responsibilities that exceed the compassion, self-denial or altruism of citizens who offered to save a fellow´s life.

Futility means that purposes cannot be achieved. Therefore, the underlying philosophy for providing CPR without waiting for any consent as an emergency outdoors procedure could be a source of controversial vulnerability for rescues today. Failure to guarantee free action of rescue team members would inevitably lead CPR Protocol to a futile fate[13].

In a cardiac arrest situation, time-pressure urges any rescue team to achieve its mission; and my particular opinion is that currently–far from universalizing a practice that has been shown to save millions of lives–the goals of treatment are subjected to conflicts from judicial companies, always attentive to finding those altruistic citizens and health professionals who cared to properly teach and learn the CPR on suspects of violating individual human rights.

As was well stated by Cotler[9], CPR is predicated on the assumption that life is sacred, as well as the efforts to maintain it, so that CPR will be successful. This seems to be really consistent with his belief that allowing someone to die is harm[13]. To establish a prognostic doubt of this universal practice –accessible to both health professionals such as doctors, paramedics, civil defense security personnel as well as lay Samaritans or relatives– will result in an unfair insecurity for potential rescuers, undermining the overall results of CPR application against the possibility of legal or financial threatening for them. Saving a life through CPR implies an altruistic, humanely ethical and disinterested practice in order to provide our fellow human beings with a new opportunity to live. It does not seem appropriate to subject professionals or volunteers to the menace of such a contingency.

It is my conviction that proposing a regional information plan prior to the application of CPR protocols would allow their consensual determinations of DNR orders in those countries in which these are in force, avoiding any dangerous restrictions that may hinder such a valuable resuscitation practice for those who need it most.

ARTICLE HIGHLIGHTS

Research background

Regarding KI-1 Yong quan application as a cardiopulmonary resuscitation (CPR) revival point, divulgation was not limited to actuarial cardiac results, but KI-1 Yong quan function as a brain protector in both traumatic and vascular brain injury situations should be included. Needless to say, all patients subjected to the stimulation of KI-1 Yong quan by cardiac arrest were neurologically classified with 3 points on the Glasgow Scale. Likewise, the validation of this CPR complementary rescue maneuver, deepening its significance of certainty respect to current techniques and protocols still in force. The difference obtained was also confirmed to be statistically significant, adding to this analysis the F-test for dichotomous variables; thus, all the statistical validations demonstrated once more the relevant certainty before other methods currently used instead of KI-1 Yong quan maneuver. Maybe such assertion led the Chinese to conclude that both KI-1 Yong quan and PC-9 Zhong chong acupuncture points had the ability to "reset" the vital signs that are absent, as a battery that would provide us with a source of alternative vital energy if our own existence is under severe danger.

Research motivation

The current figures produced by the COVID-19 pandemic and its respective mutations are close to 125000000 infected and 3000000 deaths. Faced with such a panorama, it is evident that the application of life support protocols in the extra-hospital setting is hardly exceeding 6.4%. Even those not specialized in the subject can easily realize that the survival results are extremely poor. The success of CPR - an authorized medical maneuver in laypersons properly prepared for it - depends crucially on the application of such a protocol by the general population to improve survival rates. Consequently, the main reason for this work is to offer an alternative available to the public worldwide and to help resolve the current success figures in CPR without risk of contagion.

Research objectives

The clear objectives already exposed are upgrade current survival rates in global CPR

thanks to the aid of this complementary resuscitation maneuver. On the other hand, there is a genuine intention of the author to relocate Traditional Chinese Medicine within the global context of existing therapeutic possibilities in emergency situations. The work justifies - after an uninterrupted investigation of the author for almost 40 years - that Chinese Medicine can deservedly share its place with Western Medicine in CPR protocols globally. Let us remember that CPR is the only authorized medical practice in those laypeople duly authorized to exercise said practice.

Research methods

As to its statistical verification, several sequences of survival rates were presented, the first 7 of which were published in Health (2015), the 8th one in the *World Journal of Critical Care Medicine* (2016) and the 9th and last sampling, at the Health Care Summit Congress in Dublin (2018). Its value actually strives in the differential detail if the deceased patients group is considered the control group instead of the patients that may be deceased group. Thus, the possibility of combining the indiciary or semiotic paradigm with the Retrospective Cohort Study allows us to manage potential lethal effects which are collateral to the random process in cases of extreme emergencies.

Research results

Strictly speaking, with 14 deaths out of 89 cases after applying this complementary rescue praxis has proven that its extra-hospital survival rates are 8 times higher than the best out-of-hospital survival rates (84.27% success).

Research conclusions

The KI-1 Yong quan complementary resuscitation maneuver, systematized since 1987, has been consistently performed in sudden death and cardiac arrest conditions as a final resource upon both basic and advanced CPR failure. After almost thirty years of experience, the author herein provides a reasoned survival bio-energetic circuit based on a detailed methodological–statistical analysis of the Wondrous Vessels (Qi jing ba mai) participating in it. The divulgation of K-1 emergency therapeutic possibilities looks for its inclusion into Critical Care Protocols, in order to upgrade survival rates in both cardiac arrest and stroke victims worldwide.

Research perspectives

Close to a total of 125000000 infections and 3000000 deaths in the world, the author believes that it is appropriate to urgently submit to medical science this easy-to-apply KI-1 Yong quan/PC- 9 Zhong chong resuscitation maneuver as a contingency measure in the face of such a catastrophe global that involves zero cost. Even without a pandemic, it is estimated that after 2020 the number of deaths from cardiac arrest and sudden death could reach 30000000 deaths per year, a figure equivalent to suffering the genocide of 50 Hiroshima bombs or 126 tsunamis Indonesia-like.

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REFERENCES

1 **Inchauspe A**. Traditional Chinese medicine K1 Yongquan and resuscitation: another kind of "Lazarus phenomenon". *Resuscitation* 2010; **81**: 505-506 [PMID: 20083334 DOI: 10.1016/j.resuscitation.2009.12.009]
2 **International Liaison Committee on Resuscitation**. International Liaison Committee of Resuscitation; [cited 23 April 2021]. igshare [Internet]. Available from: https://ilcor.org
3 1: Introduction to the International Guidelines 2000 for CPR and ECC. *Circulation* 2000; **102** Suppl 1: I-1–I [DOI: 10.1161/circ.102.suppl_1.I-1]
4 **Inchauspe AA**, Tachini D. 'Resuscitator': Golden medtech proposal introducing a new era for CPR. *J Acute Dis* 2020; **9**: 137-144 [DOI: 10.4103/2221-6189.288590]
5 **Inchauspe AA**. Drawing the Yongquan protocol into the different stages of the cardiopulmonary resuscitation sequence. *World J Crit Care Med* 2013; **2**: 17-20 [PMID: 24701412 DOI: 10.5492/wjccm.v2.i3.17]

6 **Bester J**, Kodish E. Cardiopulmonary Resuscitation, Informed Consent, and Rescue: What Provides Moral Justification for the Provision of CPR? *J Clin Ethics* **30**: 67-73 [PMID: 30896446]

7 **Inchauspe AA**, Inchauspe M. "Yongquan Maneuver´s Odyssey: Current Validation of Its Significance of P Through the Fisher's Exact Test for Dichotomous Variables". *Acta Scientific Paediatrics* 2019; **2**: 53-60. [DOI: 10.31080/ASPE.2019.02.0114]

8 **World Medical Association**. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191-2194 [PMID: 24141714 DOI: 10.1001/jama.2013.281053]

9 **Cotler MP**. The "do not resuscitate" order; clinical and ethical rationale and implications. *Med Law* 2000; **19**: 623-633 [PMID: 11143894]

10 **Ali Ali B**, Fortún Moral M, Belzunegui Otano T, Reyero Díez D, Castro Neira M. [Scales for predicting outcome after severe trauma]. *An Sist Sanit Navar* 2017; **40**: 103-118 [PMID: 28303032 DOI: 10.23938/ASSN.001]

11 **Heart Rhythm Disorders Society**. Sudden Cardiac Arrest; [cited 23 April 2021]. In: upbeat [Internet.] Available from: https://upbeat.org/heart-rhythm-disorders

12 **National Center for Education in Maternal and Child Health - Georgetown University**. International SIDS rates, ordered from lowest to highest SIDS Rate; 2013 [cited 23 April 2021] [Internet.] Available from: https://www.ncemch.org/suid-sids/statistics/

13 2: Ethical Aspects of CPR and ECC. *Circulation* 2000; **102** Suppl 1: I-12–I [DOI: 10.1161/circ.102.suppl_1.I-12]

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